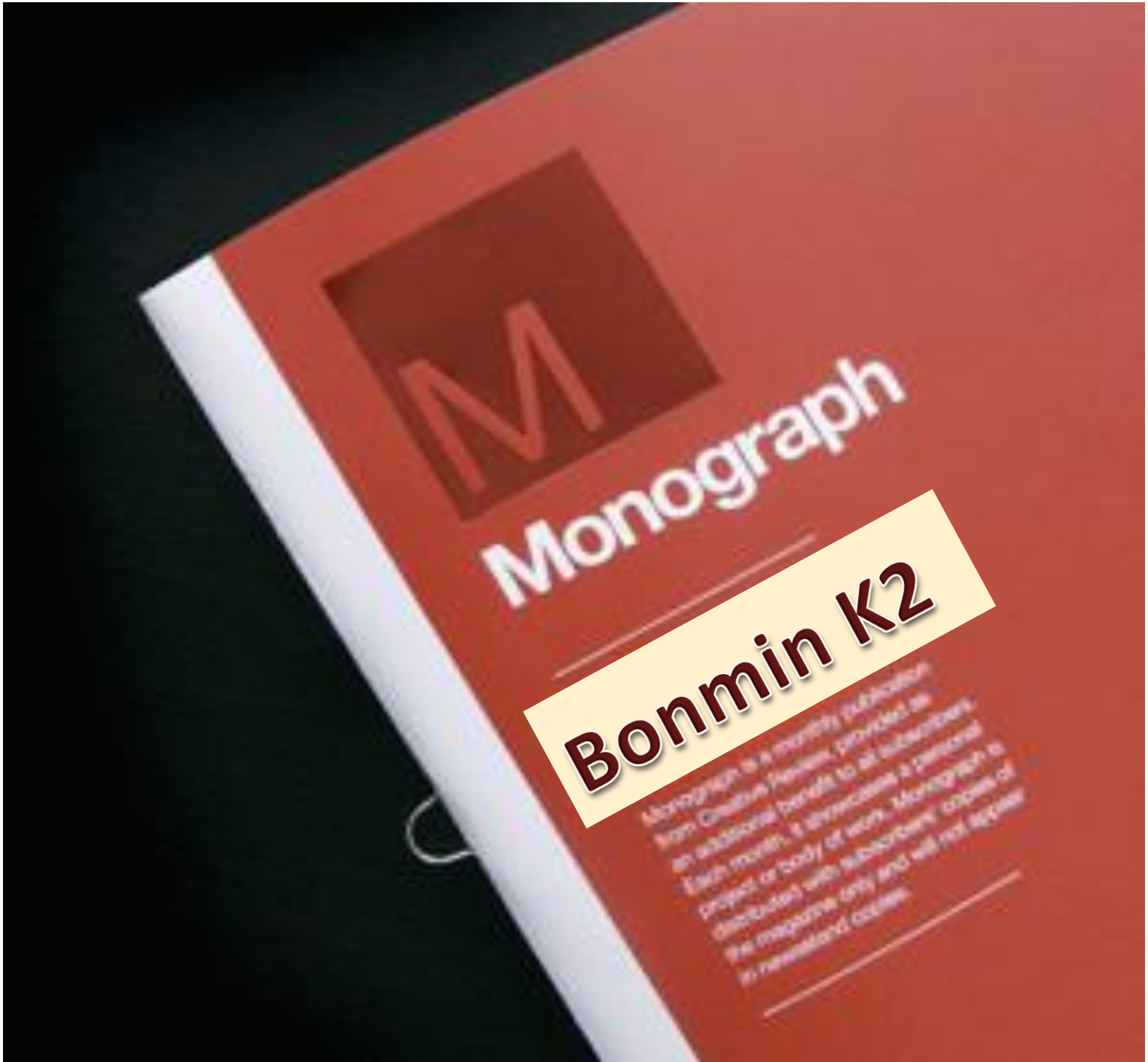

Monograph
Bonmin K2

Osteoporosis

- Major global health condition
- Associated with significant morbidity, mortality, and socioeconomic burden.
- The term osteoporosis was coined by Johann Lobstein but the disorder he described was osteogenesis imperfecta.
- In 1940, American physician and endocrinologist Fuller Albright described postmenopausal osteoporosis

Cosman F. *et al* Osteoporos Int. 2014; 25(10): 2359–2381
Malhotra N *et al.* Indian J Med Res 2008 Mar 1;127(3):263.

Osteoporosis

Initially, prevalence of osteoporosis was explained by the loss of bone mass associated with normal aging.

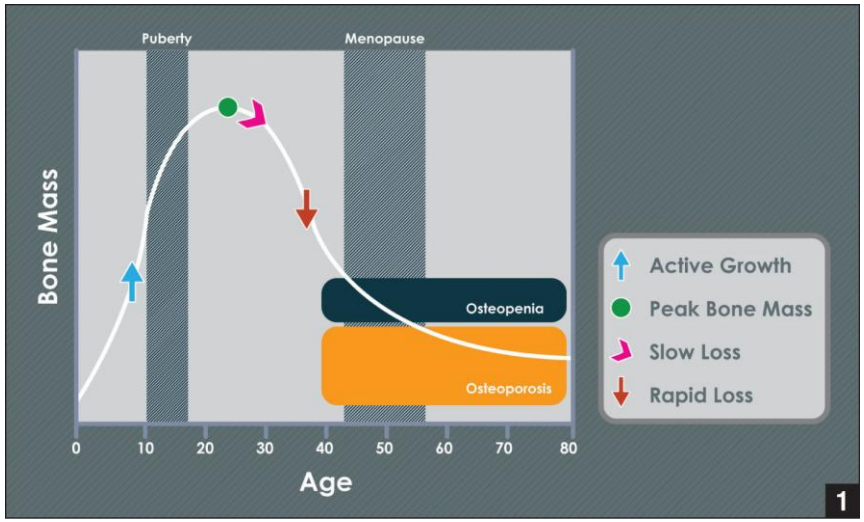


Fig. : Bone mass life cycle

Current concept

•Osteoporosis represents a continuum.

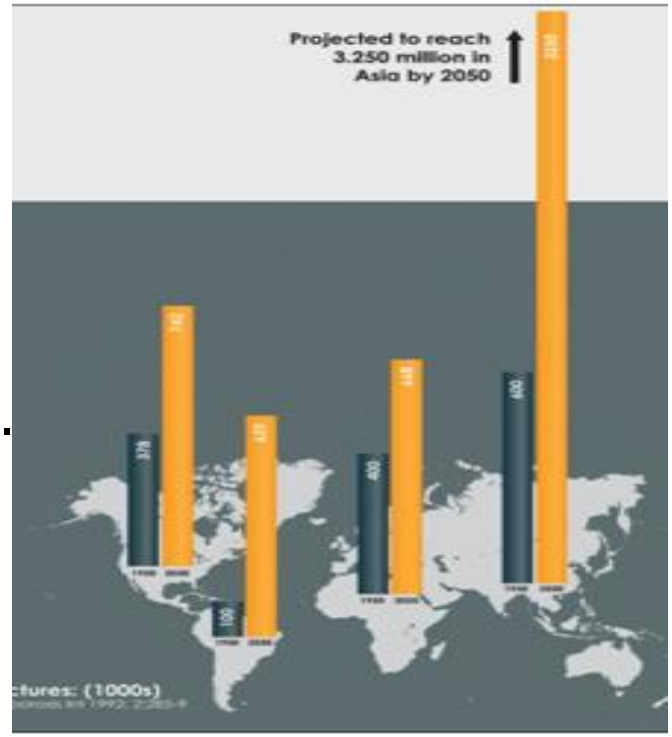
•Multiple pathogenetic mechanisms leads to loss of bone mass and micro-architectural deterioration

•These factors, coupled with an increased risk of falls, contribute to a high incidence of fragility fractures in osteoporotic patients

Shuler FD *et al.* Orthopedics 2012 Sep; 35(9): 798-805
Raisz LG et al J Clin Invest. 2005 Dec 1; 115(12): 3318–3325.

Global Burden

- Causes >8.9 million fractures annually
- Affects 200 million women worldwide
- Osteoporotic # in patients >50 years affects 1 in 3 women and 1 in 5 men.
- Vertebral and Hip # are most common.
- ≈1.6 million hip # occur worldwide each year
- By 2050, this number could reach 6.3 million

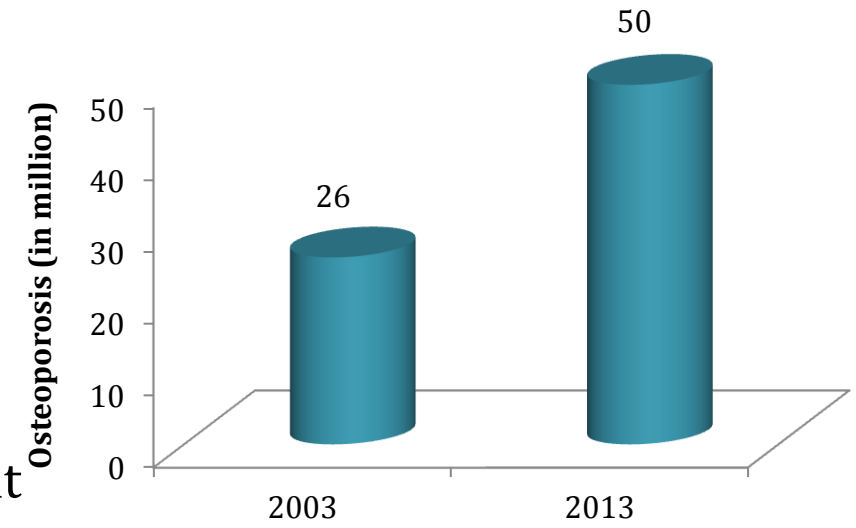


Shuler FD *et al.* Orthopedics 2012 Sep; 35(9): 798-805
Cosman F. et al Osteoporos Int. 2014; 25(10): 2359–2381

Indian Scenario

- ≈10% of India's population (more than 100 million) is aged >50 years.
- The number of osteoporosis patients in India has doubled within a decade (fig).
- Bone mineral density (BMD) at all skeletal sites: much lower than values reported from developed countries

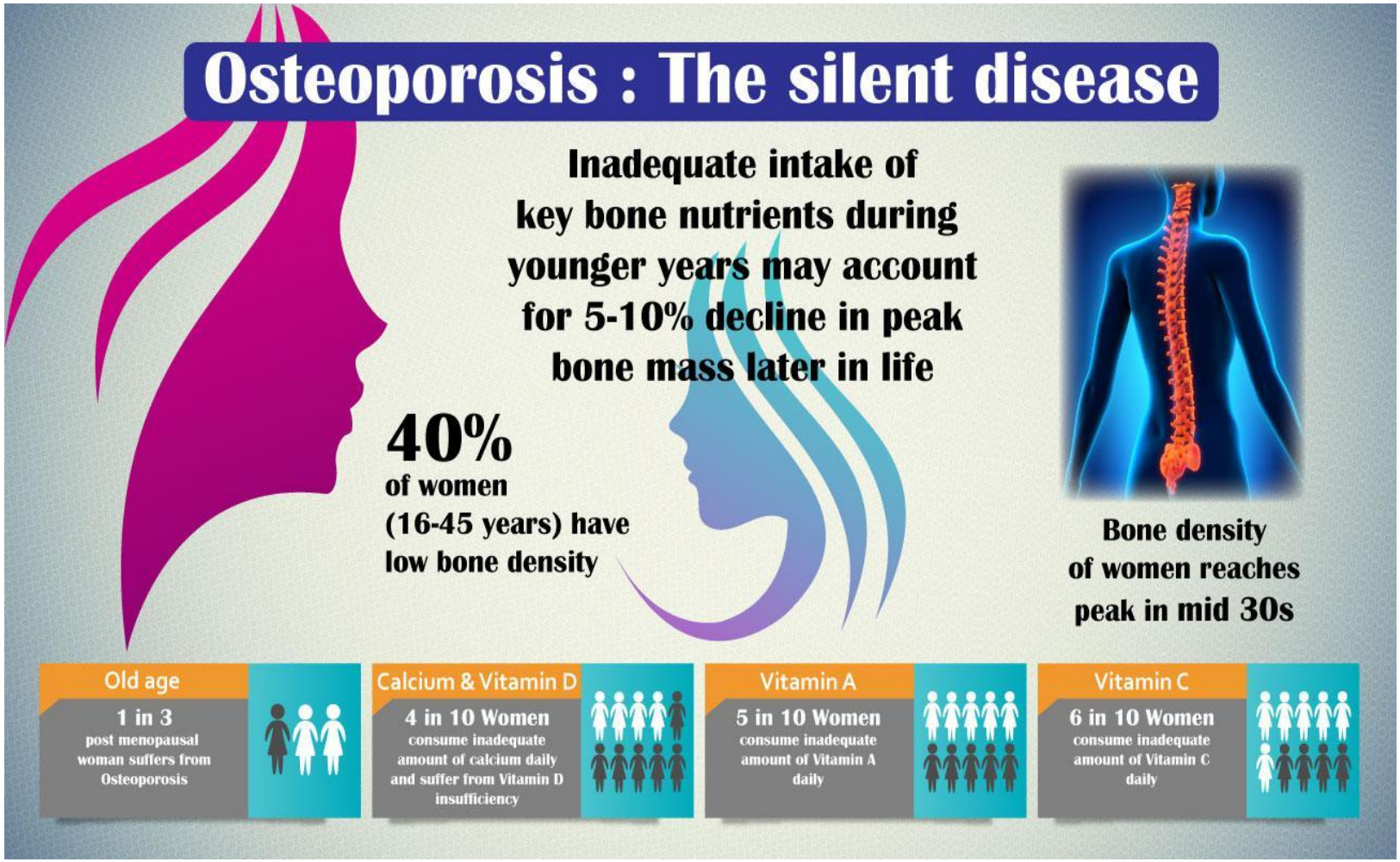
Fig. : Osteoporosis burden



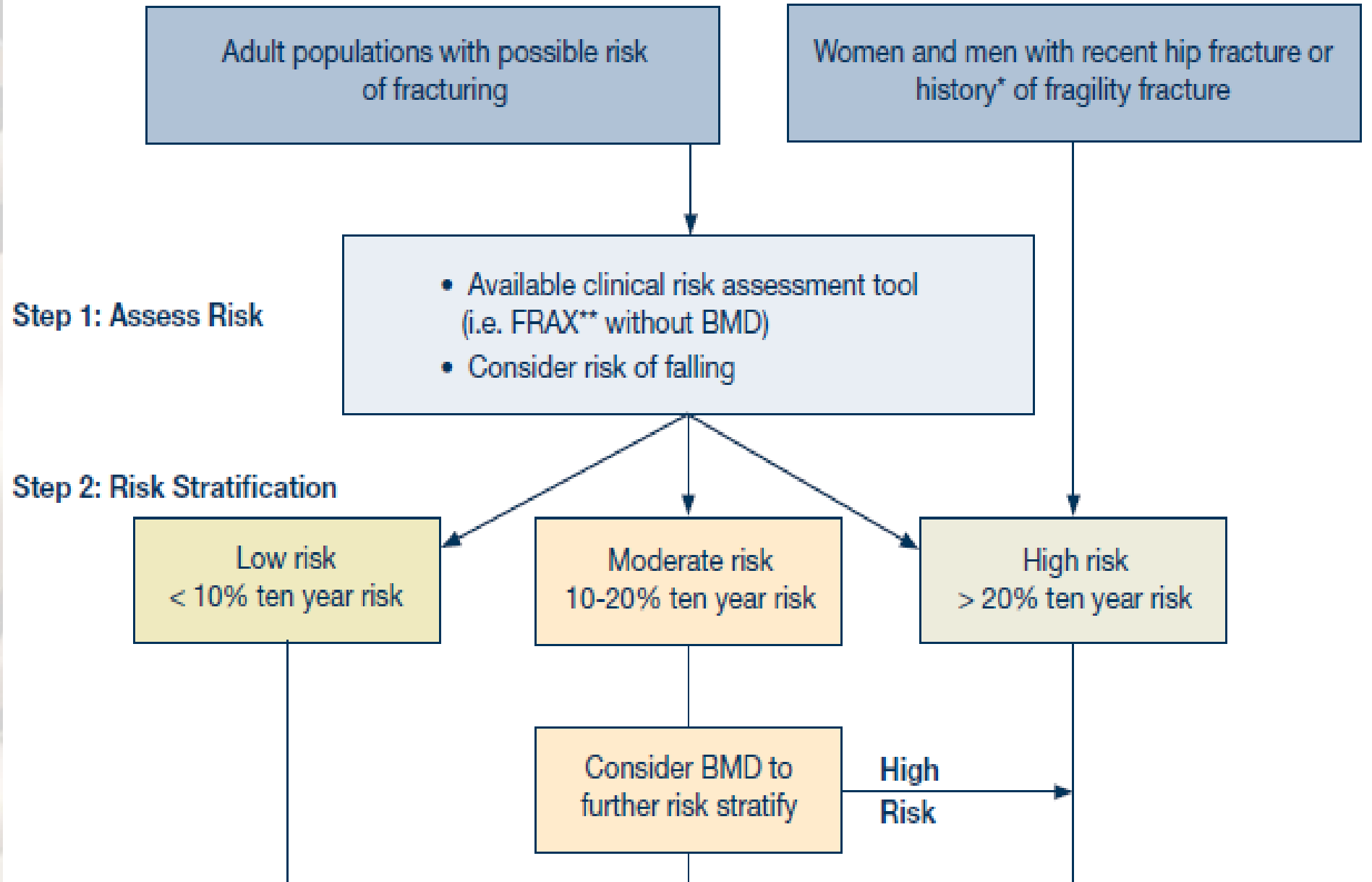
Mithal A *et al.* Indian J Endocr Metab 2014;18:449-54

Osteoporosis in Women

- An alarming rise has been noted in women being diagnosed with osteoporosis.
- Prevalence of osteoporosis range from 8% to 62% in Indian women of different age groups

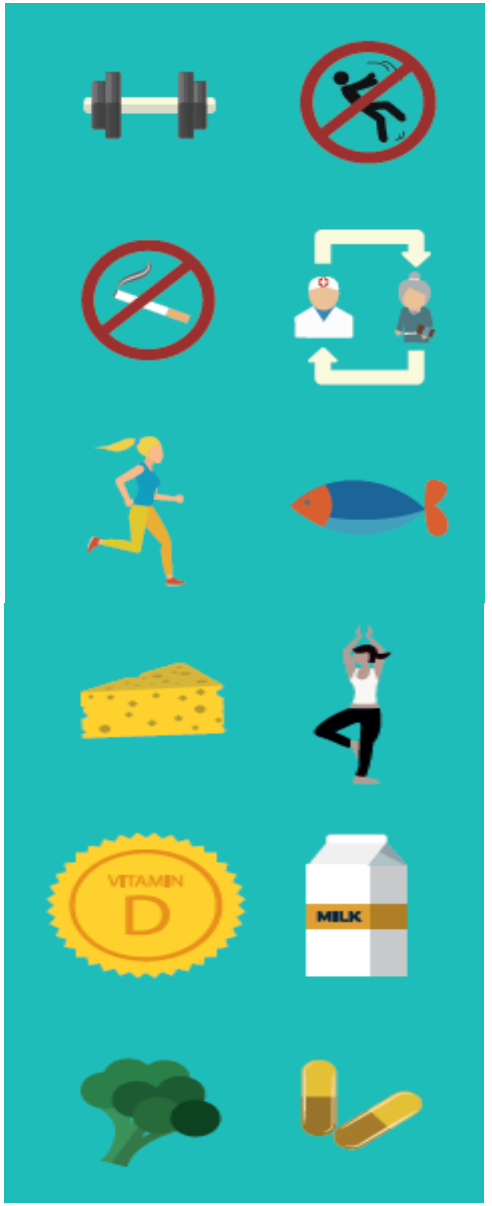


Osteoporosis Evaluation



Nonpharmacologic Approaches

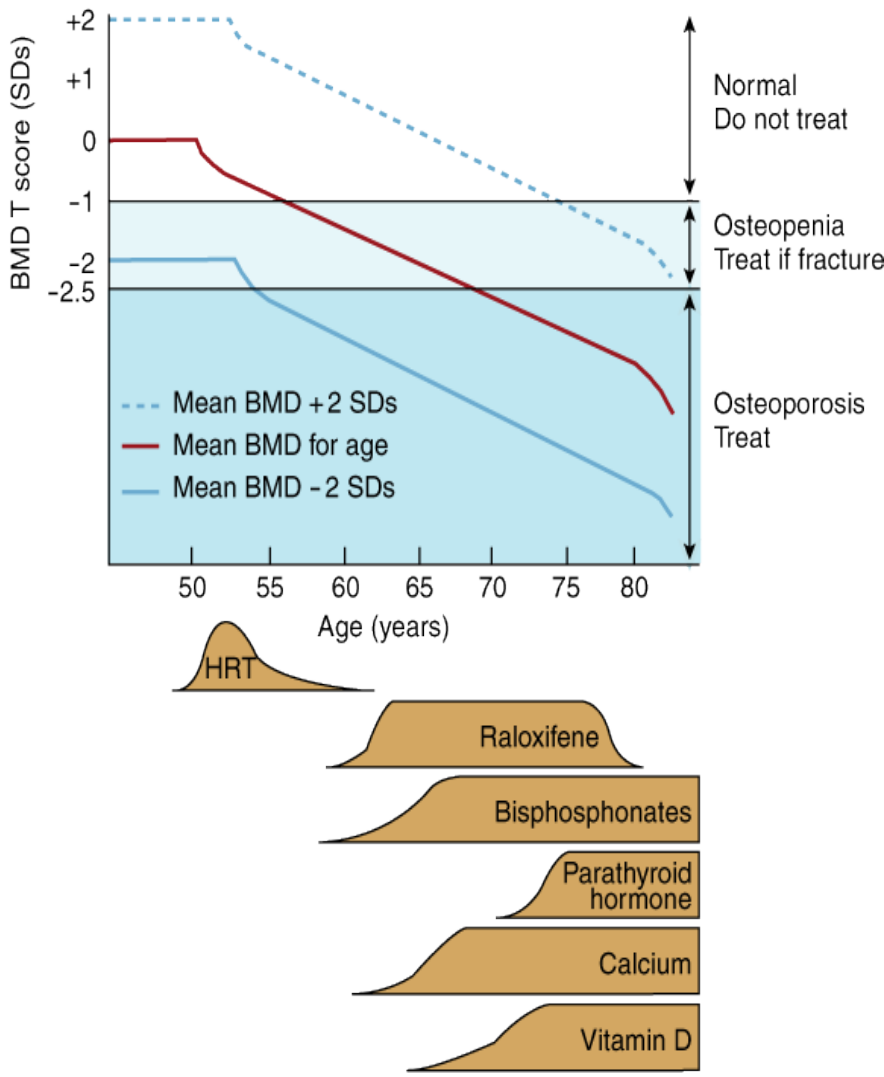
- Calcium intake.
  - Diet and/or supplementation: 1200 mg/day
- Vitamin D supplementation
  - Diagnose and treat deficiency/insufficiency.
  - Supplement: 400-800 IU/day.
- Regular load-bearing and muscle-strengthening exercise (no weight lifting if BMD in spine is low).
- Fall prevention advice.
- Avoid use of tobacco
- Limit alcohol consumption
- Consider use of hip protectors



BCGuidelines.ca: Osteoporosis - Diagnosis, Treatment and Fracture Prevention (2012)

An Approach to Treatment for Patients with Osteoporosis

■ If BMD is > 1 SD, do not treat; if BMD is 1 to 2.5 SD, treat if fracture is present; if BMD is < 2.5 SD, treat whether or not a fracture is present.
■ Consider hormone replacement therapy around menopause if patient has postmenopausal symptoms.
■ Raloxifene or one of the bisphosphonates is appropriate in the later postmenopausal years.
■ Use bisphosphonates in women aged over 75 years when the main concern is preventing hip fracture.
■ Parathyroid hormone should be considered in patients with severe osteoporosis and fractures.
■ Advised calcium supplements in people aged over 65 years, and vitamin D if deficiency is present or likely.



Osteoporosis Algorithm

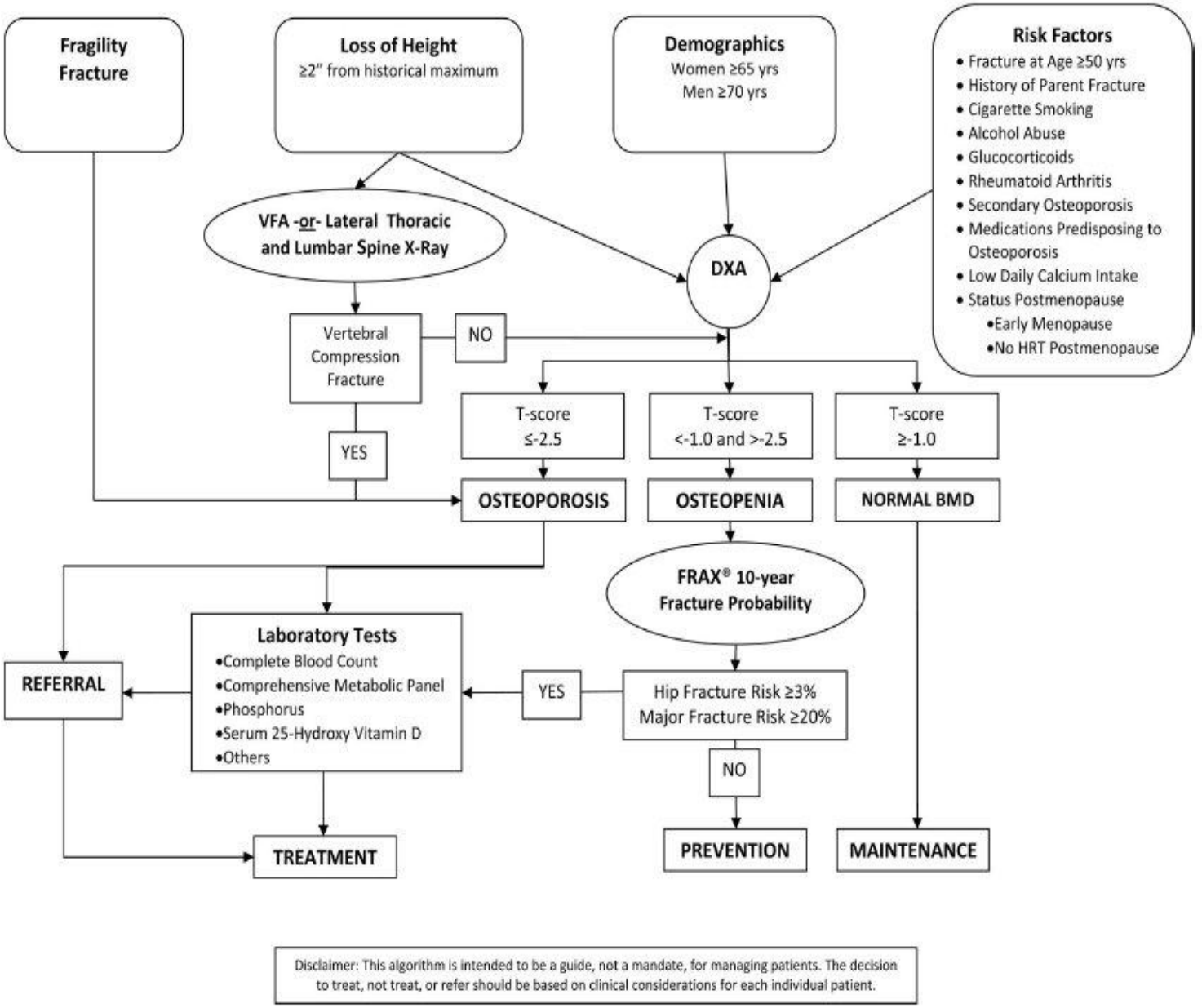


Fig. Osteoporosis Algorithm. VFA, Vertebral Fracture Assessment; DXA, dual energy x-ray absorptiometry test; HRT, hormone replacement therapy; FRAX®, World Health Organization Fracture Risk Assessment Tool; BMD, bone mineral density.

Role of Nutrition

- Adequate nutrition plays a major role in the prevention and treatment of osteoporosis
- Nutrients of greatest importance are Calcium, Vitamin D, Vitamin K27
- Prevents bone loss, decreases bone turnover, and decreases fractures
- Reports published from various international authorities including :
  - The European Commission's Report on Osteoporosis in the European Community: Action for Prevention;
  - The U.S. Surgeon General's Report on Bone Health and Osteoporosis;
  - The World Health Organization's report on Diet, Nutrition and the Prevention of Chronic Diseases

Have stressed the importance of calcium, vitamin D, and other micro nutrients including vitamin K in promoting bone health.

Nieves JW et al. Am J Clin Nutr 2005;81(suppl):1232S–9S
Cashman KD et al. J. Nutr. 137: 2507S–2512S, 2007

BONMIN K2

Composition:

Calcium Aspartate	1120 mg
Vitamin K2-7	45mcg
Zinc	7.5mg
Pyridoxal-5-Phosphate	0.5mg
L-Methylfolate	1mg
Mecobalamin	1500mcg
Magnesium	50mg
Calcitriol	0.25mcg

Role of Calcium in Osteoporosis

- Adequate calcium intake is critical to
  - achieving optimal peak bone mass and
  - modify the rate of bone loss associated with aging.

- Over the past decade, convincing evidence has emerged with respect to effects of dietary calcium on bone health in all age groups.

- Numerous studies have evaluated the relation between calcium intake and bone density.

- Higher calcium intakes leads to higher bone mass in children, young adults, and postmenopausal women - 64 out of 86 observational epidemiologic studies.

- Meta-analysis of 20 studies : Calcium supplementation can decrease bone loss by ≈1% per year

Ho SC et al. J Clin Endocrinol Metab 2004;89:2166–70.
Suzuki Y et al. J Nutr Health Aging 2003;7:296–9.

Calcium Salts

- Calcium doesn't exist by itself in the nature. It always in the form of a compound.
- Common calcium salts are Calcium Aspartate, calcium carbonate and calcium gluconate, calcium citrate etc.
- Calcium products are made from algae (seaweed), coral reefs, oyster shells, egg shells,rocks, limestone, are composed of calcium carbonate.
- Calcium carbonate is one of the most popular calcium compound. But it's also the least absorbable calcium compound.
- **Calcium aspartate anhydrous, is an organic calcium compound extracted from land-based plants.**

Kressel et al. G. *Food and Nutrition Sciences*, 2010;1(2):53-58.

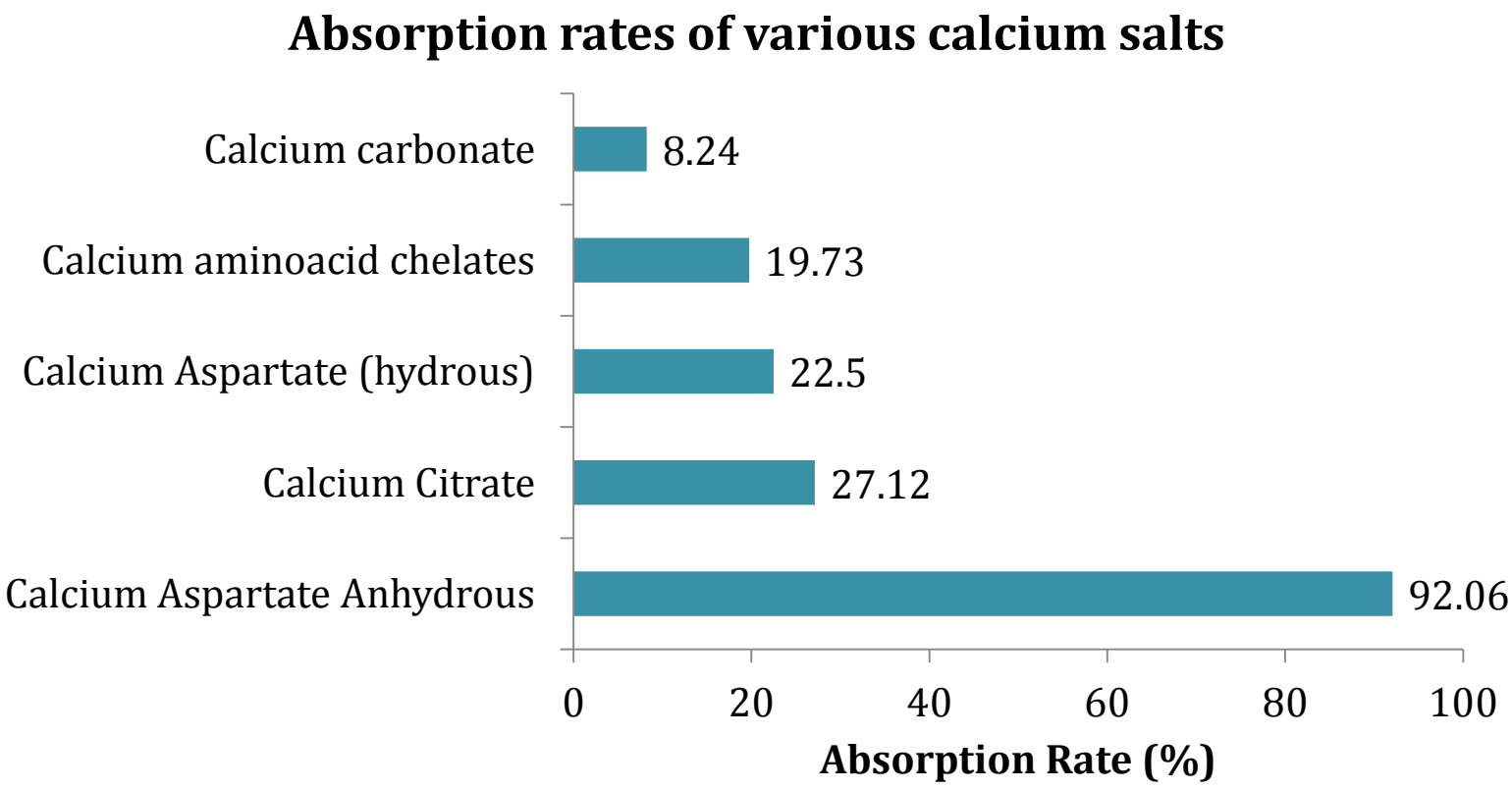
Calcium Salts

- For calcium supplements to be absorbed by body, they have to be soluble in the luminal fluid of the small intestine.
- The pH of the small intestinal fluid below the duodenum is 7.0-7.2.
- Inorganic calcium supplements will form insoluble hydroxides and become nonabsorbable in this pH range.
- Calcium aspartate, on the other hand, is well shielded by l-aspartic acids and will not precipitate.
- **As a result, Calcium aspartate has high absorption rate , 3-9 times higher than that of calcium carbonate or calcium citrate.**

Source: Available at https://ezorbcalcium.com/html/ezorb_information.html. accessed on 05-08-16

Calcium Aspartate Absorption Rate

- Calcium aspartate has absorption rate as high as 92%



Source: Available at https://ezorbcalcium.com/html/ezorb_information.html. accessed on 05-08-16

Calcium Aspartate Uniqueness

- Calcium aspartate anhydrous, is an organic calcium compound extracted from land-based plants.
- Calcium aspartate has absorption rate as high as 92%
- Maintains its chemical integrity in the small intestine and remains bioavailable.
- Prevents gastrointestinal distress.
- Does not affect absorption of other vitamins.
- Increases bone density by stimulating osteoblast activities and enhancing collagen production.

Tang JF *et al. Available at* http://www.advancedalternativescenter.com/Articles.asp?ID=202. *Accessed on 05-08-2016*

Efficacy of Calcium Aspartate Anhydrous *vs* Calcium Citrate in the management of Osteoporosis

- A multicenter, double placebo, double blind study verified the effects of calcium aspartate anhydrous on osteoporosis.

- Patients with T-score under –1.5, were randomly assigned to three groups:
  - Group I receives calcium aspartate (4 g/ day, 520 mg elemental) and a placebo matching Vitamin D.
  - Group II receives calcium citrate (1,500 mg elemental per day) and Vitamin D (1000 IU/day).
  - Group III was given one placebo matching calcium and another placebo matching Vitamin D.

Tang JF *et al. Available at* http://www.advancedalternativescenter.com/Articles.asp?ID=202. *Accessed on 05-08-2016*

Results

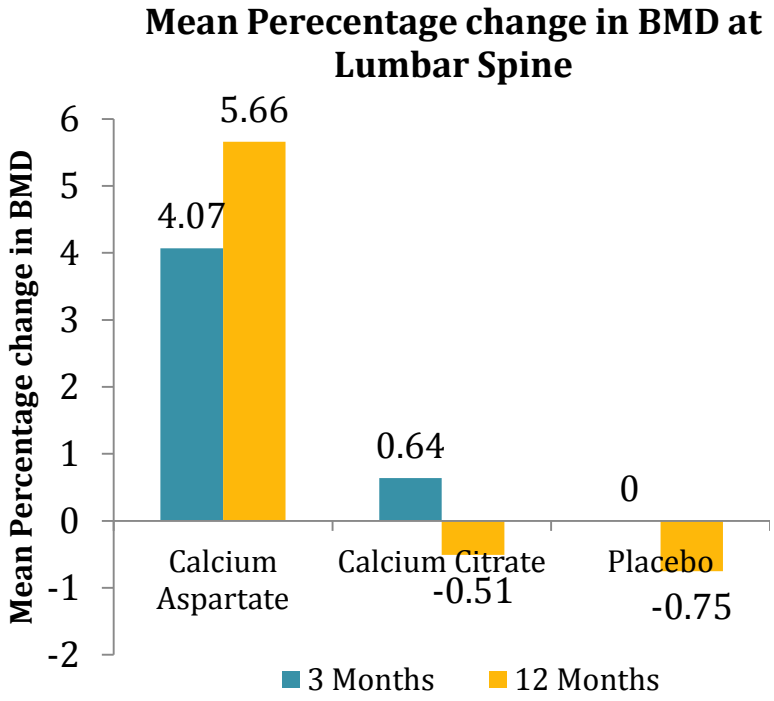
- At 3 months, BMD at the lumbar spine had increased by a mean of 4.07% in the Cal AA group.

- At 12 months, lumbar spine BMD had increased by a mean of 5.66 percent in the CalAA group, while the calcium citrate group and the double-placebo group saw decline of 0.51% and 0.75% respectively.

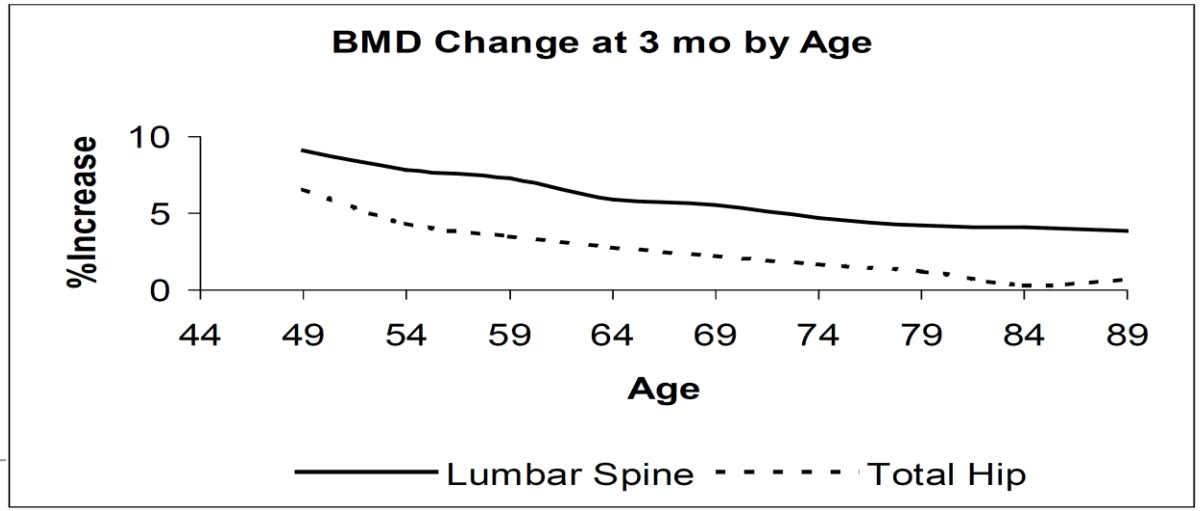
- The BMD of total hip had increased by mean of 3.37 % in the CalAA group.

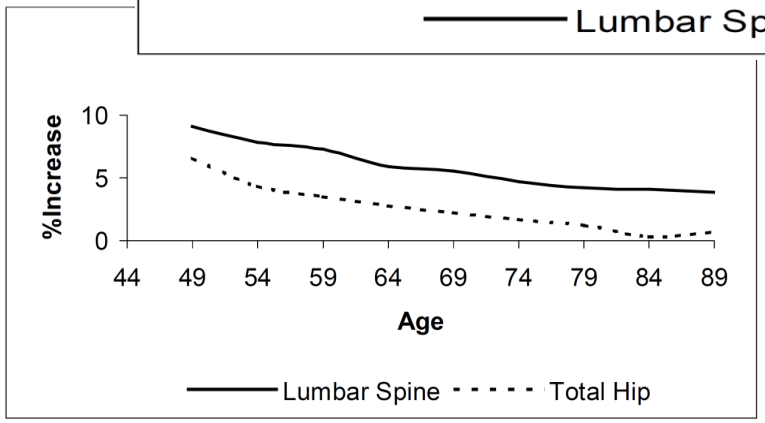
- Total hip BMD had increased by mean of 4.11 % in Cal AA group

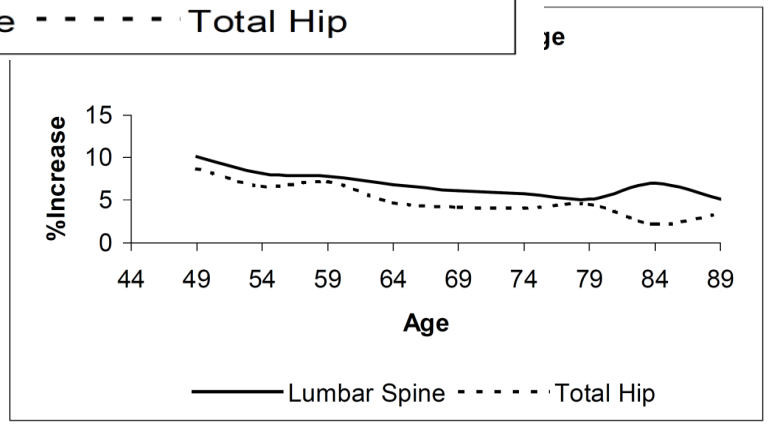
- Total hip BMD declined by a mean of 1.17% in double-placebo group.



Results





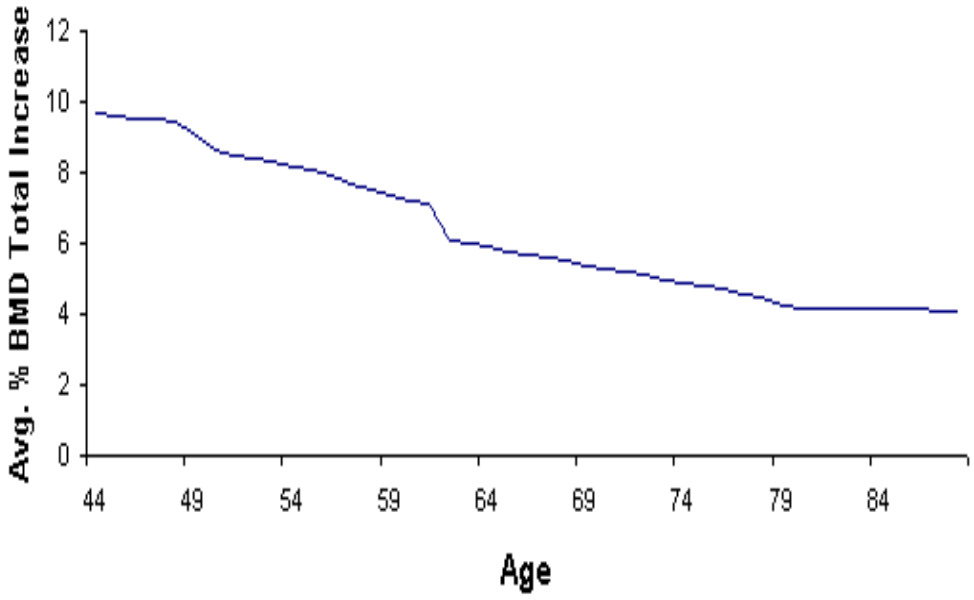


Calcium aspartate is better than Calcium Citrate in the management of Osteoporosis

Tang JF *et al. Available at* http://www.advancedalternativescenter.com/Articles.asp?ID=202. *Accessed on 05-08-2016*

Calcium Aspartate Anhydrous in the management of Osteoporosis

In another study, the calcium aspartate was found to increase the BMD after 3 months

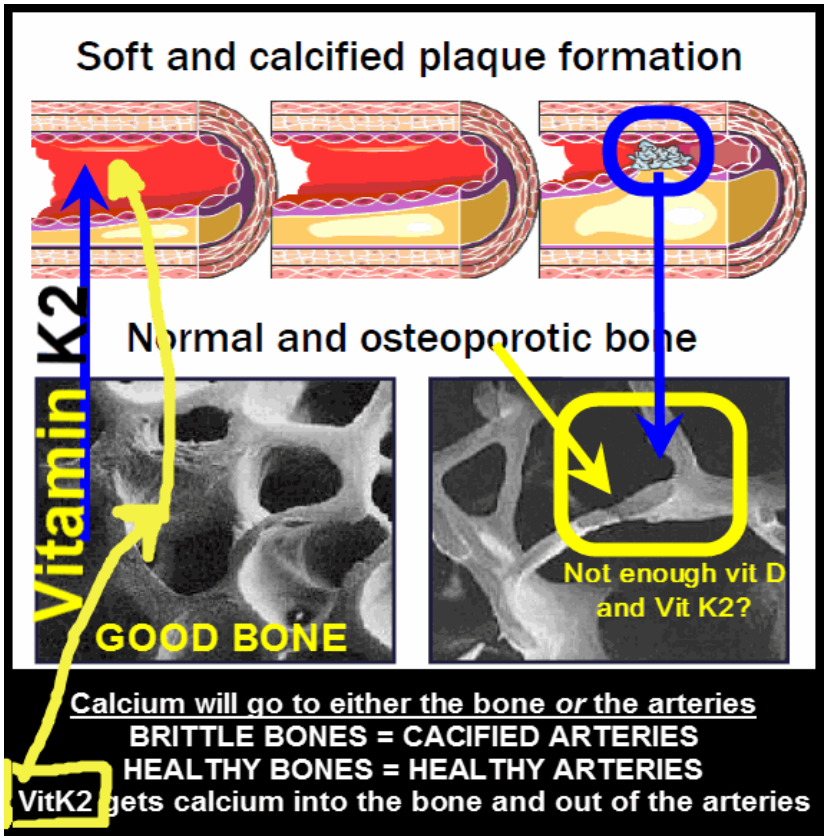


Calcium aspartate anhydrous increases bone mineral density and an effective therapeutic option in the management of Osteoporosis

Source: Available at https://ezorbcalcium.com/html/ezorb_information.html. accessed on 05-08-16

Vitamin K27

- Vitamin K2 (the menaquinones) is a group name for a family of related compounds.
- Vitamin K27 deficiency is associated with osteoporosis and increased risk of fracture.
- Vitamin K27 has a dual role in mediating bone homeostasis
- Vitamin K sufficiency activates carboxylated proteins and promotes calcium homeostasis.



Asrar F et al. IJPR 2014;4(2): 43-48

Vitamin K27

- Vitamin K27 is an essential cofactor for γ-carboxylase.

- Vitamin K-dependent (VKD) protein carboxylation uses Vitamin K epoxidation to convert Glus to carboxylated Glus (Glas), rendering VKD proteins active in physiologies that include:
  - hemostasis,
  - apoptosis,
  - bone mineralization,
  - calcium homeostasis,
  - growth control, and
  - signal transduction.

- Vitamin K27 deficiency results in incomplete γ- carboxylation of osteocalcin (OC) and matrix Gla protein (MGP) associated with osteoporosis and increased risk of fracture.

Asrar F et al. IJPR 2014;4(2): 43-48

Vitamin K27

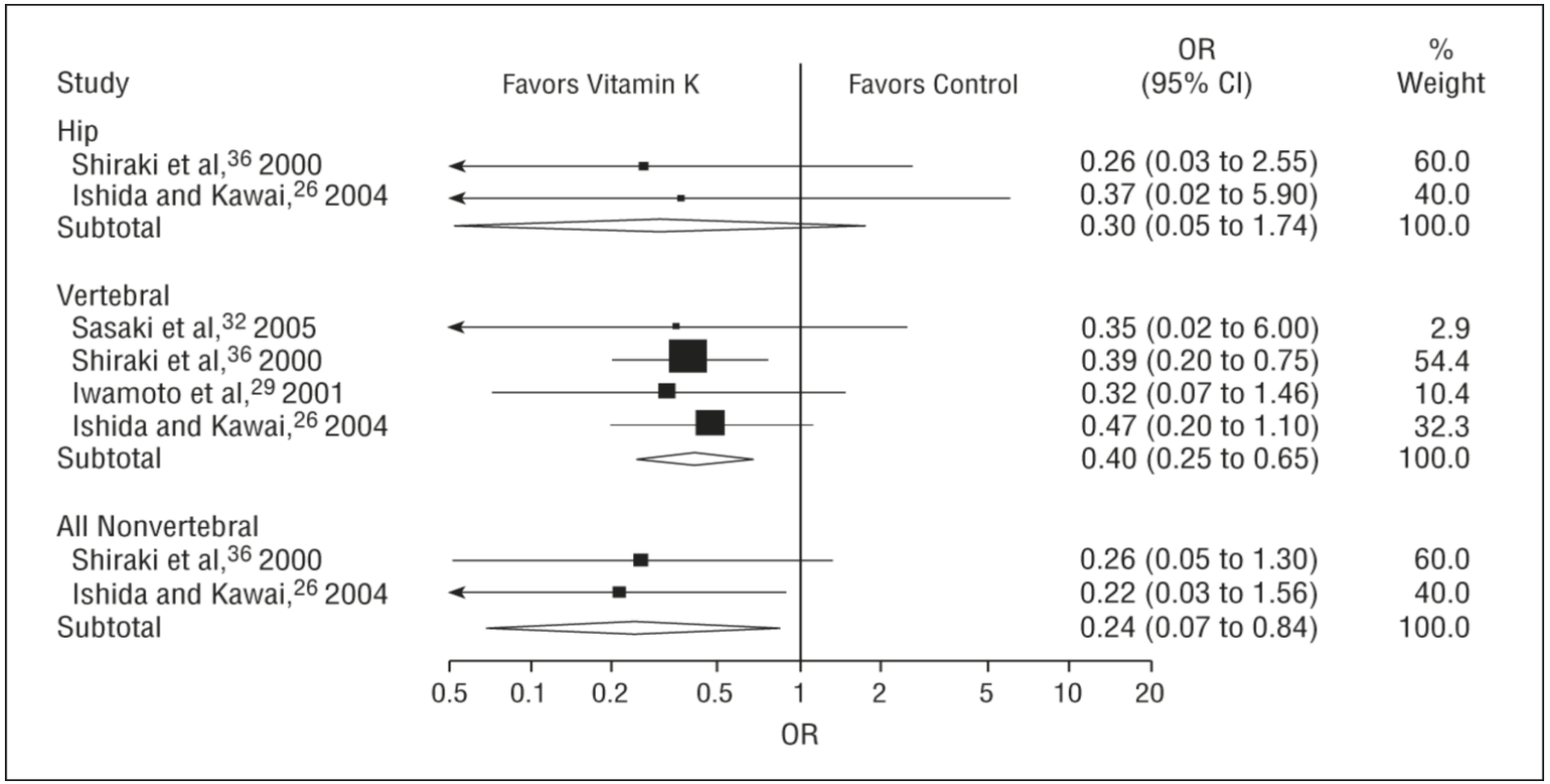
- Vitamin K27 has a dual role in mediating bone homeostasis.
- It acts in an anabolic manner to stimulate the synthesis of osteoblastic markers and deposition of bone.
- Vitamin K27 decreases bone resorption by inhibiting the formation of osteoclasts as well as their bone resorptive activity.
- Vitamin K27 treatment also induces apoptosis of osteoclasts while inhibiting apoptosis of osteoblasts thereby shifting the balance towards bone formation.
- Vitamin K27 enhances the induction of OC (Osteocalcin) mRNA levels mediated by coadministered 1α, 25(OH)2 Vitamin D.

Asrar F et al. IJPR 2014;4(2): 43-48

Vitamin K and the prevention of fractures

- In a meta-analysis Cockayne S et al. assessed the vitamin K role in reducing bone loss and prevent fractures.

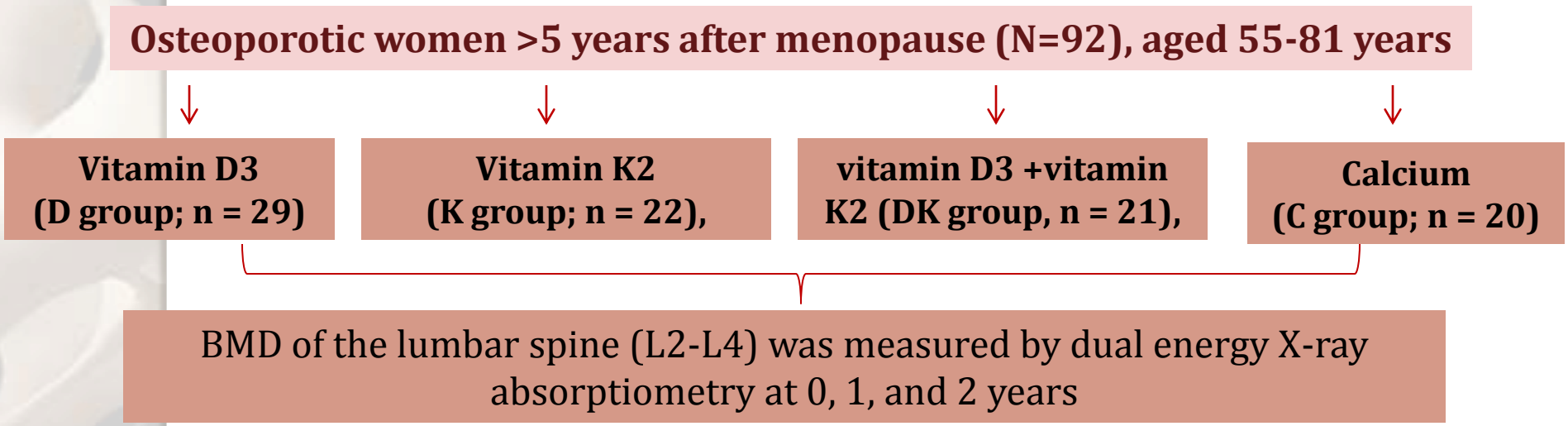
- Menaquinone supplementation has also been shown to effectively improve markers of bone health, although it is important to note that the doses of menaquinones used could not be achieved via the diet.



Cockayne S et al. Arch Intern Med. 2006 Jun 26;166(12):1256-61.

Vitamin K2 in osteoporosis

- Efficacy of combination of Vitamin K2 with D was evaluated in primary osteoporosis.
- Combined administration of Vitamin D and Vitamin K2 seems to have the greatest effect on lumbar bone mineral density.



RESULTS: A significant increase in BMD in the DK group compared with that in the C, D, and K groups ($P < 0.0001$, $P < 0.05$ and $P < 0.01$, respectively).

Iwamoto J et al. J Orthop Sci. 2000;5(6):546-51.

Calcitriol

- Calcitriol is an active vitamin D metabolite.
- Plays a role in many biological processes, especially in bone metabolism and muscle function, and is mediated by vitamin D receptors.
- During the past four decades, many clinical trials investigating the effect of Calcitriol on bone loss

Liao RX et al. Clin Interv Aging. 2014; 9: 515–526.

Calcitriol Clinical Studies

Study characteristics of trials involving calcitriol and bone biomarkers

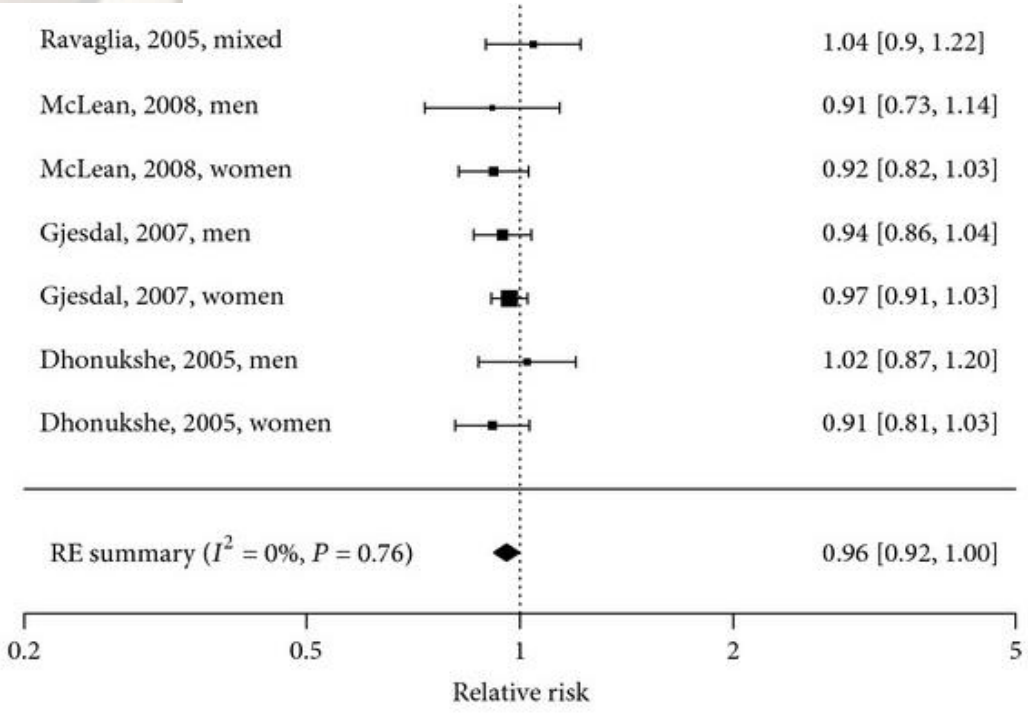
Trial	Year	Number of participants	Study population	Trial duration	Treatments	Results
Gram et al. [69]	1996	36	Healthy males	1 week	A) 2.0 µg/day Calci	PTH: A,B<C
					B) 1.0 µg/day Calci	BSAP: A,B<C
					C) Placebo	PICP: A,B>C
						CTx: NS
Sirtori et al. [77]	1996	12	Postmenopausal osteopenic women	1 week	A) 1.0 µg/day Calci	PTH: Post A<Pre A
					B) 0.5 µg/day Calci	PTH: Post B<Pre B
						Osteo: Post A>Pre A
						Osteo: Post B/Pre B, NS
						BSAP: Post A/Pre A, NS
						BSAP: Post B/Pre B, NS
Tsukamoto et al. [80]	2003	18	Postmenopausal women	4 weeks	A) 0.5 µg/day Calci	NTX: A<B
					B) Control	PTH: A<B
						BSAP: NS
Aloia et al. [65]	1988	27	Postmenopausal osteoporotic women	2 years	A) 0.8 µg/day Calci+800 mg calcium	PTH: NS
					B) 400 IU/day Vit D+800 mg calcium	
Caniggia et al. [66]	1986	25	Postmenopausal osteoporotic women	6–30 months	A) 1.0 µg/day Calci	Osteo: Post A>Pre A
Caniggia et al. [67]	1990	270	Postmenopausal osteoporotic women	1–8 years	A) 1.0 µg/day Calci	Osteo: A>B
					B) Historical Controls	
Gallagher et al. [68]	1982	18	Postmenopausal osteoporotic women	6–8 months	A) 0.5 µg/day Calci	BFR: A>B
					B) Placebo	BRR: A<B
Inanir et al. [70]	2004	70	Postmenopausal osteoporotic women	6 months	A) 0.5 µg/day Calci + 1,000 mg calcium	PTH: NS
					B) 1,000 mg calcium	IL-1: A<B
						IL-6: NS
						TNF-α: A<B
Lambrinoudaki et al. [71]	2000	81	Premenopausal women with lupus	2 years	A) 0.5 µg/day Calci + 1,200 mg calcium	ALP: B>A, C
					B) Placebo Calci + 1,200 mg calcium	

Peppone LJ et al. Osteoporos Int. 2010 Jul;21(7):1133-49

Mecobalamin

- Emerging evidence suggests a protective association of Vitamin B12 and folic acid.
- Main determinants for low bone mineral density:
  - High concentrations of homocysteine
  - Low levels of Vitamin B12 and folate,

Higher risk of fractures in the elderly



Longitudinal observational studies including 7475 elderly people with 3 to 16 years of follow-up addressed the association between serum/plasma vitamin B12 and fracture

van Wijngaarden JP et al. J Nutr Metab. 2013; 2013: 486186

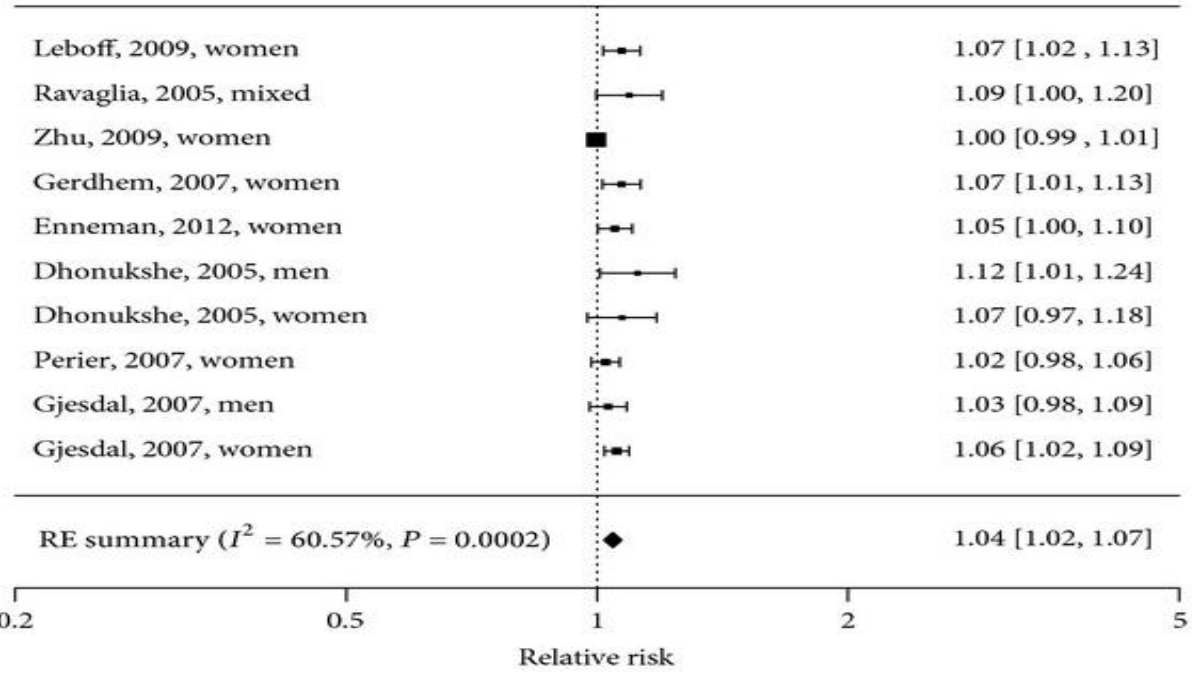
Pyridoxal-5-Phosphate

- Pyridoxalphosphate (PLP) is active or coenzyme form of vitamin B6.
- PLP contains three natural organic compounds pyridoxal, pyridoxamine and pyridoxine.
- PLP has the capacity to lower body's levels of homocysteine.
- Plasma homocysteine (Hcy), is formed by the demethylation of dietary methionine,
- Homocysteine is a risk factor of osteoporotic fractures.
- High plasma total homocysteine levels are associated with accelerated bone loss in men and premenopausal women

Ruan J *et al.* Med Sci Monit. 2015; 21: 875–881

L-Methylfolate

- Primary biologically active form of folic acid
- Used at the cellular level for DNA reproduction, the cysteine cycle and the regulation of homocysteine
- B vitamins involved in homocysteine conversion, such as B12, and folate (folic acid), may be beneficial in reducing risk of osteoporosis



11 longitudinal observational studies examined the association between homocysteine status and fracture incidence

Fratoni V et al. Nutrients. 2015 Apr; 7(4): 2176–2192.
van Wijngaarden JP et al. J Nutr Metab. 2013; 2013: 486186

Experimental evidence on B vitamins and bone health

References	Study Model	Treatment (T) *vs.* Control (C)	Bone Outcomes	Main Findings
Murray *et al.* 1977 [10]	Chick cartilage *in vitro*	T: Isonicotinic acid hydrazide *vs.* C: (G-31H) pyridoxine hydrochloride to chick embryos	Lysyl oxidase activity	Decreased lysyl oxidase activity in cartilage and aorta in treatment chicks *vs.* controls.
Fujii *et al.* 1978 [11]	Rats	T: B6 deficient diet *vs.* C: 30 mg/100 g B6 fed diet	Collagen cross-linking formation	B6-deficient rats had more soluble bone collagens, lower amount of aldehydes and collagen formation.
Bird *et al.* 1982 [12]	*In vitro* embryotic chick aorta	T: PLP added C: no treatment to illuminated lysyl oxidase	Lysyl oxidase activity	The presence of PLP increased enzyme activity. The removal of PLP decreased enzyme activity.
Dodds *et al.* 1986 [13]	Rats	T: B6 deficient diet *vs.* C: 6 mg/kg pyridoxine hydrochloride	Bone formation	Vitamin B6-deficiency reduced G6PD activity in bone formation and callus development. B6-deficient fed rats had more osteoporotic bones with cavities and less new bones.
Masse *et al.* 1994 [14]	Chicks	T: 0.4 mg/kg *vs.* C: 3 mg/kg B6 to young chicks	Bone mechanical property	Deficient chicks had decreased cortical thickness, osteoid in trabecular bone, reduced secondary ossification centers and coarse trabeculation.
Masse *et al.* 1996 [15]	Chicks	T: 0.4 mg/kg *vs.* C: 3 mg/kg of B6	Bone mechanical property and collagen cross-linking	Deficient chicks had decreased fracture load and offset yield load, and increased collagen solubility.
Herrmann *et al.* 2009 [16]	Rats	T: a folate- and B12-deficient diet *vs.* C: standard diet for 12 weeks	Homocysteine level, bone strength (femoral neck compression), bone area, BTM: OC and CTx	Higher plasma homocysteine level in T group *vs.* controls, but no difference for homocysteine concentration in the bone tissue. No difference in bone strength, bone area, or BTM.
Herrmann *et al.* 2007 [17]	Human osteoblasts	Three B vitamins, B6 and folate (μg/L), B12 (ng/L) at various concentrations (0, 0.1, 10, 100, 1000)	Alkaline phosphatase, OC, and P1NP activity; Mineral matrix for formation	No significant difference for BTM levels or mineral matrix among different concentrations of a mix of three B vitamins. Homocysteine level is significantly higher in all concentrations except at the highest concentration of three B vitamins.

Observational studies on B vitamins and bone health

References	Study Populations/ Follow-up Time	Exposures	Outcomes	Effect of B Vitamins	Main Findings
Abrahamsen *et al.* 2005 [23]	1700 Danish postmenopausal women	Dietary intake of B2, B6, folate and B12	BMD	Yes: B2, B6, folate, and B12	B2 is the only significant predictor among the B complex for FN BMD in the TT genotype. Lowest quartile of B2, B6, folate and B12 intake reduced BMD in the TT genotype.
Golbahar *et al.* 2005 [24]	366 postmenopausal Iranian women	RBC 5-MTHFR	BMD	Yes: Folate	RBC 5-MTHF predicted BMD, but not plasma 5-MTHF.
Morris *et al.* 2005 [25]	1500 U.S. White men and women	Serum and RBC folate, serum B12 and homocysteine	BMD; Osteoporosis prevalence risk	Yes: B12; No: Folate	No association was found between folate and BMD or osteoporosis. Significant risk observed in the lowest quartile of B12 *vs.* the highest quartile. A positive relationship between B12 and BMD when B12 < 220 pmol/L.
Baines *et al.* 2007 [26]	328 postmenopausal British women	Plasma homocysteine, serum folate, B6, B12 and MTHFR genotypes	BMD	Yes: Folate; No: B6 and B12	Folate significantly related to BMD. B6, folate and B12 significantly related to homocysteine level. Homocysteine appeared to be related to BMD.
Holstein *et al.* 2009 [27]	94 German men and women	Fasting serum folate, B6, B12	BTM: OC, TRAP; BMD, trabecular thickness, number, and area.	Yes: B6, folate, B12	OC is lower in those with low level of B vitamins. Trabecular thickness and area are lower in those with low folate. Trabecular number is lower in those with low B6. No association between B vitamins and BMD or homocysteine.

Longitudinal Studies

References	Study Populations/ Follow-up Time	Exposures	Outcomes	Effect of B Vitamins	Main Findings
Dhonukshe-Rutten *et al.* 2005 [33]	615 men and 652 women aged 76 (SD 6.6) years/ 3 years	Homocysteine, B12 status and the combined effect	Broadband ultrasound attenuation; BTM: OC and of DPD/Cr and fracture risk	Yes: B12	Women with B12 < 200 pM and homocysteine > 15 μM had lower BUA, higher DPD/Cr, and higher OC. No differences in men between the different level of homocysteine and B12. High level of homocysteine and/or low level of B12 increased risk by 2.8 and 3.8 folds in men and women, respectively. Lowest quartile of B12 increased fracture risk in women only. Highest quartile of homocysteine significantly increased fracture risk in men.
Ravaglia *et al.* 2005 [34]	702 Italians aged 65–94 years/4 years	Serum folate, B12 and homocysteine	Fractures	Yes: Folate; No: B12	Higher level of homocysteine increased fracture risk. Lowest folate quartile had 2-fold increased risk *vs.* higher quartiles, but no dose-respondent relationship. No association between B12 and fracture risk.
Tucker *et al.* 2005 [35]	2576 U.S. White men and women 30–87 years	Plasma B12	BMD at total hip, trochanter, Ward's area, and femoral neck and at lumbar spine (cross-sectional analysis)	Yes: B12	A positive relationship between plasma B12 and BMD at hip in men, and at the lumbar spine for women.
Macdonald *et al.* 2004 [31]	1241 Scottish women aged 45–54 years/6.6 years	Dietary intake of B2, B6, folate and B12	BMD; BMD change; BTM, fPYD/Cr and fDPD/Cr and serum P1NP	Yes: B2; No: B6, folate and B12	B2 intake significantly related to BMD in subjects with *MTHFR TT* homozygotes. No associations found in BMD change or BTM, nor in *CC* or *CT* genotypes. No associations were found in other B vitamins.
Stone *et al.* 2004 [32]	83 U.S. White women 65+ years from a subset/3.5 and 5.9 years	Serum B12	BTM: BAP, osteocalcin; hip BMD and calcaneal bone mass.	Yes: B12	Women at lower serum B12 ≤ 280 pg/mL had higher rate of bone loss from the hip than those at B12 > 280 pg/mL. No association was found with site BMD or BTM.

Randomized clinical trials on B vitamins and bone health outcomes

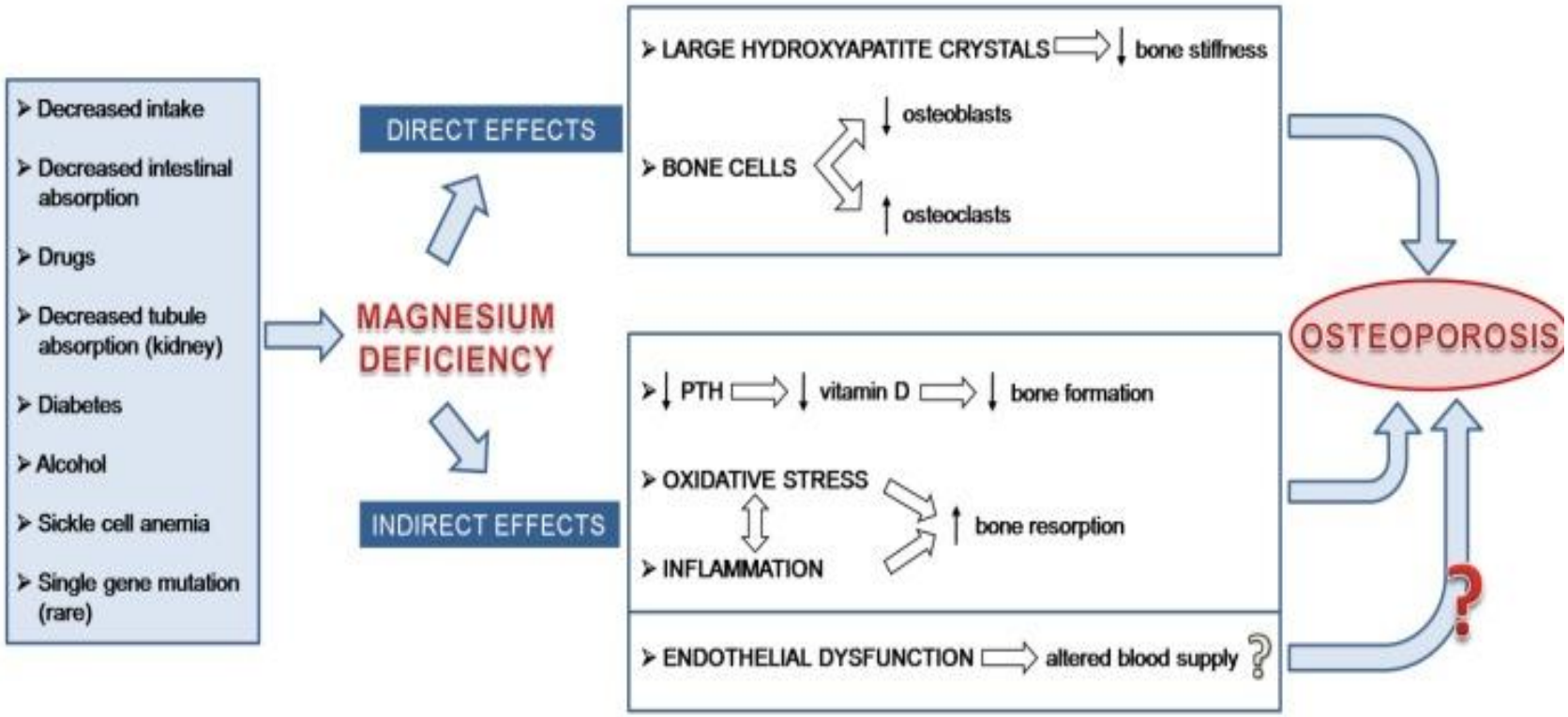
References	Study Populations/ Follow-up Time	Treatment (T) *vs.* Control (C)	Outcomes	Effect of B Vitamins on Bone Outcomes	Main Findings
Sato *et al.* 2005 [43]	628 aged 65+ years patients with residual hemiplegia after stroke for 1 year+/2 years	T: Daily treatment with 5 mg folate and 1500 μg B12 for 2 years	Plasma homocysteine, hip fracture incidence	Yes: folate and B12	After two years, treatment group had lower homocysteine and placebo group had higher homocysteine. Hip fracture incidence was significantly reduced in treatment group. No difference in BMD.
Herrmann *et al.* 2006 [44]	61 healthy individuals aged 58 years (SD 8)/8 weeks	T: 0.4, 1 or 5 mg folate daily; C: placebo.	Serum HCY, folate, B12; BTM: OC, P1NP, and CTX.	No: folate	T *vs.* C: Folate increased, homocysteine decreased. No difference in BTM.
Green *et al.* 2007 [45]	267 healthy individuals aged 65 year+/2 years	T: 1 mg folate, 500 μg B12 and 10 mg B6; C: Placebo	Plasma homocysteine, BAP, CTx	No: folate, B6 and B12	Lower homocysteine in T *vs.* C group; no significant difference for serum BAP or CTx
Shahab-Ferdows *et al.* 2012 [46]	132 aged 20–59 years Mexican women/3 months	T: B12 1 mg i.m. then 500/day orally ($n = 70$); C: placebo ($n = 62$).	Serum B12, folate, MMA, holoTC, homocysteine; BTM: BAP	No: B12	Supplementation of B12 increased holoTC and lower MMA and homocysteine. But no difference found in BAP.
Gommans *et al.* 2013 [47]	8164 Caucasian with recent stroke or transient ischemic attack/2.8 year's therapy and 3.4 years follow-up.	T: Daily 2 mg folate, 25 mg B6 and 500 μg B12 ($n = 4089$); C: Placebo ($n = 4075$)	Fracture risk; Serum homocysteine	No: folate, B6 and B12	No significant difference in fracture risk between two groups. Homocysteine was lower in treatment group, but it did not predict fracture risk.
Keser *et al.* 2013 [48]	31 Croatian women aged 65 years+ with homocysteine >> 10 μmol/L/4 months	T: 800 μg folate and 1000 μg B12 ($n = 17$) daily, C: Placebo ($n = 14$)	BTM: ALP and CTx	No: folate and B12	Treatment group had significantly lower homocysteine and higher serum folate or B12; But no difference in serum level of ALP or CTx.
van Wijngaarden *et al.* 2014 [49]	2919 Dutch aged 65 years with elevated homocysteine (12–50 mmol/L)/2 years	T: Daily 500 μg B12 and 400 μg folate with 600 IU D3 C: placebo with 600 IU D3.	Serum homocysteine, First time fracture	Yes: folate and B12 in 80 years+	Homocysteine significantly lower in the treatment group. Fracture risk did not differ between two groups. But significant lower risk was found in those 80 years+ in the treatment group. However, a higher risk of cancer also observed in the treatment group.
			Meta-Analysis		
					4% borderline significant decreased fracture risk per 50 pmol/L increase in B12, which was

Zinc and Magenesium

- Zinc has stimulatory effect on osteoblastic bone formation and mineralization.
- Zinc inhibit osteoclastic bone resorption due to inhibiting osteoclast-like cell formation from bone marrow cells and stimulating apoptotic cell death of mature osteoclasts
- Dietary zinc intake and plasma zinc each have a positive association with BMD in men.

Magnesium

- Magnesium deficiency contributes to osteoporosis directly by acting on crystal formation and on bone cells and indirectly by impacting on the secretion and the activity of parathyroid hormone and by promoting low grade inflammation



Magnesium and zinc status in osteopenic and osteoporotic patients

- Studies have shown that dietary intake of magnesium, zinc in post-menopausal women with low bone density are significantly lower than recommended dietary allowance.

- The mean serum levels of zinc (P = 0.001) and copper (P = 0.000) were significantly lower than normal.

- Supplementation with magnesium, zinc, copper stimulates osteoblasts and bone mineralisation.

Mahdavi-Roshan M et al. Clin Cases Miner Bone Metab. 2015 Jan-Apr; 12(1): 18–21.

The Effective Combination

- Calcium aspartate anhydrous, is an organic calcium compound
- Calcium Aspartate in this combination is known for its superior calcium absorption rate (92%) and bioavailibility
- Calcium Aspartate does not affect absorption of other vitamins
- Calcium aspartate increases bone density by stimulating osteoblast activities and enhancing collagen production.
- Vitamin K2 and Calcitriol demonstrates synergistic effects and provide better bone health.
- Pyridoxal-5-Phosphate decrease hip fracture incidence and involve in bone health
- The combination of B-12 and folate is known to lower homocysteine. Vitamin B-12 increases bone mass and density.
- Magnesium and Zinc assures the strength and firmness of bones. It is essential for absorption and metabolism of calcium.

Bonmin K2 is a comprehensive formula which contains all essential nutrients in the management of Osteoporosis.

Bonmin K2: Information Sheet

Indications

- Bonmin K2 is effective for the management of Osteoporosis

Dose and Method of Administration:

- One tablet daily

Pharmacokinetics Properties:

INGREDIENTS	ABSORPTION	DISTRIBUTION AND STORAGE	METABOLISM	EXCRETION
CALCIUM ASPARTATE	92% absorption rate	Distributed mainly in the tissues	liver	Renal quickly
CALCITRIOL	Protein binding: 99.9%	Rapidly distributed throughout the body.	Renal,5–8 hours (adults), 27 hours (children)	Faeces (50%), urine (16%)

Pharmacokinetics Properties:

INGREDIENTS	ABSORPTION	DISTRIBUTION AND STORAGE	METABOLISM	EXCRETION
VITAMIN K2-7	Rapidly and unchanged from the gastrointestinal tract	Distributed to liver, extrahepatic tissues such as cardiovascular and bone.	Metabolised in the liver	eliminated via the urine.
ZINC	Absorbed in the organs in an ionic form	60% bound to albumin. Mainly distributed to organs such as the liver, lung, and kidney	Metabolized in the liver	Excreted small part via the urine, while most were excreted via the feces
PYRIDOXAL-5-PHOSPHATE	Absorbed by passive diffusion in the jejunum and to a lesser extent in the ileum.	Primarily stored in the liver, lesser amount in the muscle and brain. Not protein bound	Metabolized in the liver.	Excreted in the urine. The t ½ is 15 to 20 days.
L-METHYL FOLATE	Peak plasma levels have been reported 1 to 3 hours following administration.	The plasma protein binding of L-methylfolate is 56%.	The mean elimination half life is approximately 3 hours.	L- methylfolate is primarily excreted via the kidneys.
MECOBALAMIN	Peak plasma concentrations after 3 hr. It is readily absorbed in distal half of the ileum	Protein binding is very high to specific transcobalamins plasma proteins.	Hepatic Biological half life Approximately 6 days (400 days in the liver).	Renal

Bonmin K2: Information Sheet

Contraindications

- Contraindicated in those hypersensitive to its ingredients,
- Hypercalcemia and hypercalciuria (e.g., in hyperparathyroidism, decalcifying tumors such as plasmocytoma, bone metastases),
- Severe renal or cardiac diseases like ventricular fibrillation.

Warnings and Precautions:

- The combination should not be used in patients who are:-
- allergic to any of its ingredient
- pregnant, planning to become pregnant, or are breastfeeding
- having liver disease or have a history of liver disease

Adverse Effects

- Loss of appetite, GI Complaints

Summary

- Osteoporosis: Inevitable consequence of aging in both sexes.
- Osteoporosis is still under diagnosed.
- Bone mineral density testing is the best available test to assess fracture risk.
- Nutritional Supplementation can be very effective in the management of Osteoporosis

Summary

- Calcium Aspartate has superior calcium absorption rate (92%) and effectively increases bone density.
- Vitamin K27 has a dual role in mediating bone homeostasis and essential for carboxylation of Osteocalcin
- Calcitriol plays critical role in reducing rate of bone loss
- Mecobalamin, L-Methylfolate, Pyridoxal-5-Phosphate lowers homocysteine levels, improves BMD and decreases the fracture risk.
- Zinc and Magnesium stimulates osteoblasts and bone mineralisation

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