




OSTEOPOROSIS AND THE LATEST NOVEL TREATMENTS

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DEFINITION:

Osteoporosis is a major, world wide, public health problem, is a systemic skeletal disease characterized by decreased bone mass and a microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures.



WHO criteria for the diagnosis of osteoporosis is characterized by BMD of > -2.5 SD below the mean value of peak bone mass in young normal women.

Osteopenia -1 SD to <-2.5 SD

Osteoporosis > -2.5 SD

Based on these it is estimated that 54% of post menopausal white women in the US have osteopenia and 30% have osteoporosis.

In the US >25 million have significantly decreased BMD and 1.5 million fractures (Vertebrae, distal radius and hip) per year.

2004 costs \$18 billion

2040 estimated \$240 billion

Maximum skeletal mass is achieved in young adults at 18-25 years of age. After age 40, slow phase of bone loss begins (0.5-1% per year) and after menopause an additional 2-3% per year because of decreasing estrogen concentrations.

Fracture risk is determined by absolute BMD, regardless of age.





Treatments:

Arginine

Xylitol

Silicon

DHEA

Exercise

Progesterone

Calcitonin

Selective Estrogen Receptor Modulators (SERM)

Androstendione

Boron

Estrogen

Manganese

Phosphorus

Testosterone

Vitamin D

Magnesium

Parathyroid Hormone

Aromatase

Isoflavonoids

Calcium

Protein

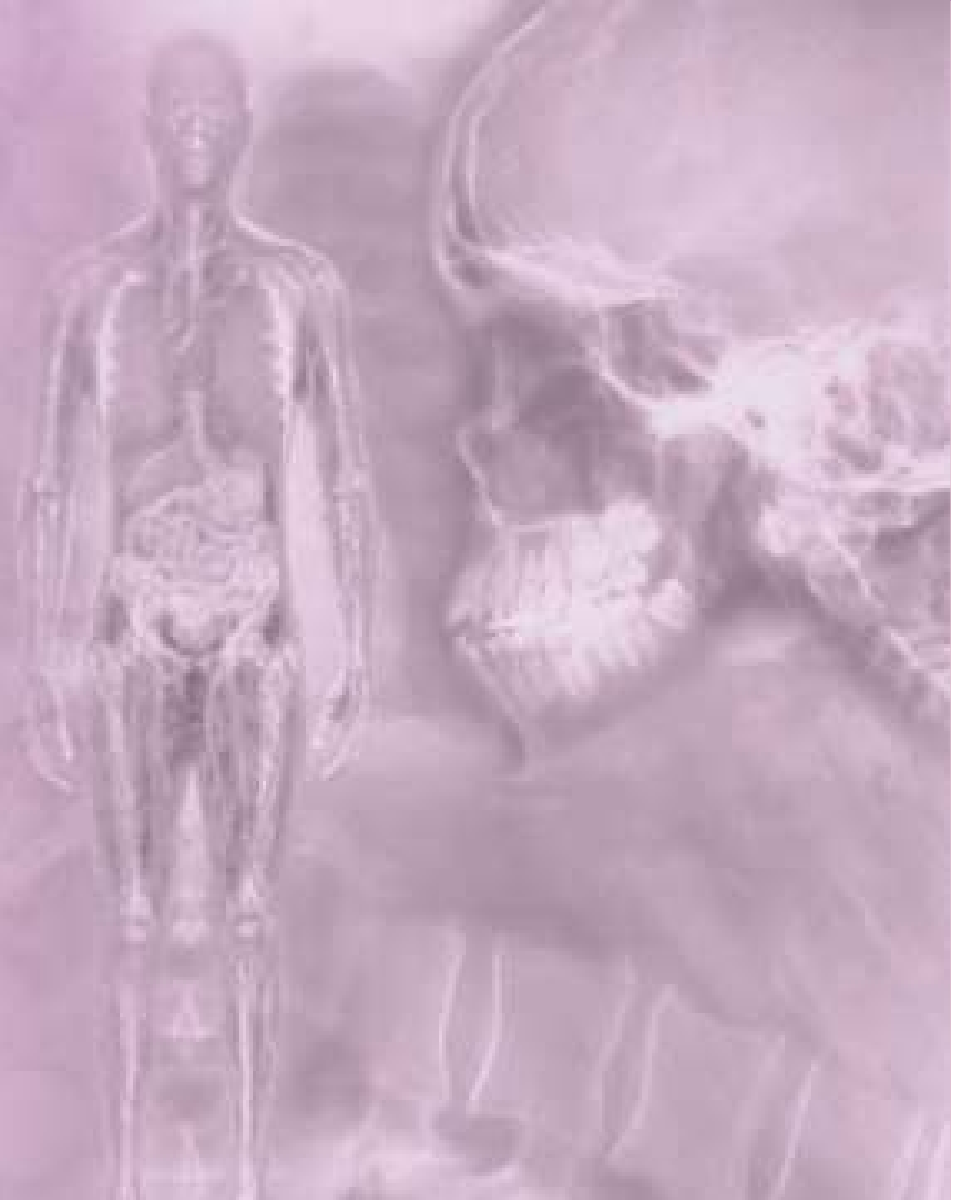
HGH

Biphosphonates



Recent Novel Treatments:

- Strontium
- Osteo Basic Protein
- Vitamin K2
(Menatetrenone)





History of Strontium:


1790: Discovered by Adair Crawford near Strontian, Scotland.


1919: Alwens. “Ueber die Beziehungen der unterernahrung zur osteoporose und osteomalazie. Muchen Med Wehnschr.

1942: Weinmann reported Strontium is vital to the development of a health skeletal system. 99% found in bone.

1949: Italian author reported areas of high strontium in water, decreased incidence of cavaties.

1949: French researchers reported deficiency of strontium in diet causes defective mineralization of the bones. Mammals need strontium for normal development.





1952: Shorr and Carter: First Clinical Trial at the Russell Sage Institute of Pathology. Strontium 1700mg elemental as lactate. 3-4 months some 4 years.

Noticed when intake of calcium was maximal, calcium retention plateaued. No more calcium retained in body

Conclusion: *Strontium supplementation improves the retention of calcium, phosphorus and protein, in women with post menopausal osteoporosis.*

Shorr E and Carter, AC. The Value of Strontium as an adjuvant to calcium in the remineralization of the skeleton in osteoporosis in man. 1952

McCaslin, FE Jr and Janes, JH. The effect of Strontium lactate in the treatment of osteoporosis Proc. Staff Meetings Mayo Clinic, 1959; 34: 329-334.

- 72 patients 1750mg as Strontium lactate 3 months – 3 years.
- No side effects observed.
- 84% “marked” improvement in subjective symptoms.





1981: Stanley Skoryna McGill University.


- Total of 142 patients
- Some Strontium **Carbonate**/
Strontium **Gluconate**
- Doses 100mg to 1.5g of salt.
Demonstrated dose response relationship.
Increased Strontium - Increased bone
mineral density.

**Skoryna, S. Effect of oral supplementation
with stable strontium. CMA Journal. 1981;
125: 703-712.**



1984: Skoryna – 6 patients

- Strontium **carbonate** 1700mg
- All patients achieved increase in BMD
- Osteoblast number increased 120%
- Rate of new bone formation increased 172%



2002: Meunier, PJ et-al. Strontium ranelate : dose-dependent effects in established postmenopausal vertebral osteoporosis – a 2 year randomized placebo controlled trial. J.Clinical Endocrinol Metab. 2002; 87: 2060-2066.

- Strontium as **ranelate**.
- 353 women with osteoporosis and at least one fall.
- Patients also on Calcium and Vitamin D3.
- Strontium dose 680mg elemental.

Group 1. Calcium and Vitamin D - lost 0.57% BMD in the hip

Group 2. Calcium and Vitamin D and Strontium

- **increased bone mass +2.97%**
- **increased +3.05% bone mineral density.**

Strontium supplemented group suffered 1/2 as many vertebral deformities compared to Calcium and Vitamin D group.



The Effect of Strontium Ranelate on the Risk of Vertebral fracture in Women. Meunier, P.J et-al. N.Engl J Med. 2004; 350: 459-468

- 1442 post menopausal women (> 50 yrs)
- Post menopausal for at least 5 years
- 3 years at least 1 spinal fracture
- Plus Calcium and Vitamin D
- BMD measured at 12 month intervals

RESULTS:

- 12 months. Risk of vertebral fracture was 49% lower (6.4% vs. 12.2%)
- Risk of having more than 1 new vertebral fracture was 6.4% in Strontium group vs. 9.8% in placebo group.
- Fewer patients in Strontium group lost 1cm or more in height (30.1% vs. 37.5%)
- BMD in the lumbar spine increased by **12.7%** in strontium group.
- Calcium and Vitamin alone – loss of 1.3% lower spinal bone mass
- Strontium and Calcium and Vitamin D – increase of 14.4% lower spinal bone mass.

To put in perspective, the powerful biphosphonate drug Fosamax increases BMD by no more than 5.5% even when combined with other therapies.





CONCLUSIONS:

Strontium

- Inhibits bone resorption
 - Promotes bone building
 - Stimulates baby osteoblasts to multiply
 - Increases production of bone matrix
 - Increases DNA synthesis
- Strontium has been used as a **chloride, carbonate, lactate, gluconate and ranelate**.
 - Ranelate is a synthetic molecule. Bioavailability is around 27% Chloride is 25%.
 - Ranelic acid contributes nothing to the effect of strontium.
 - Excreted almost exclusively >93%
 - Strontium ranelate enhanced replication of pre-osteoblastic cells
 - Calcium and sodium ranelate had no effects
 - Patent issue

Strontium Citrate

- High elemental yield
- Natural liquid
- Part of Krebs cycle
- Should have good bioavailability

Osteo Basic Protein



MILK

Useful, safe, good source
of bioavailable calcium

Functional role in
growth of newborns



MILK

3.2% Milk Proteins

Casein 81.2%

Whey Protein 18.87%

- 20% alpha lacta albumin
- 58% beta lactoglobulin
- 13% Immunoglobulin
- 7% albumin

Milk Basic Protein are basic proteins rich in lysine and arginine

Cell Proliferation of Osteoblastic cells

MBP promoted [³H] thymidine incorporation into the cells in a dose-dependent manner.

Effect of MBP on [³H] Thymidine Incorporation and PICP Contents in Osteoblastic Cells^a

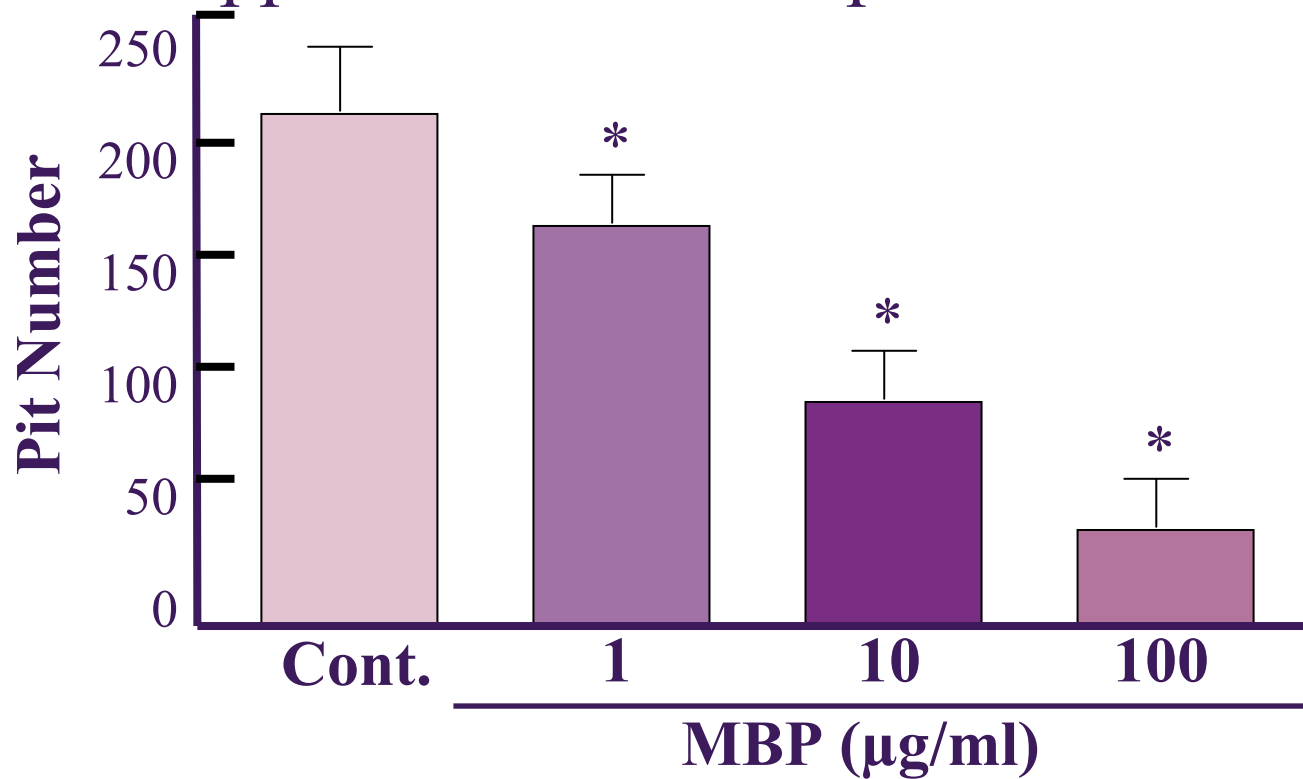
	Control	MBP ($\mu\text{g/ml}$)		
		1	10	100
[³ H]Thymidine incorporation, (cpm)	1205 \pm 316	2467 \pm 421*	2531 \pm 572*	9463 \pm 894
PICP contents, ng/ml medium	456 \pm 34	734 \pm 45*	853 \pm 79*	1324 \pm 132

^aValues are mean \pm SD

*Significantly different from the control group ($p < 0.05$)

Effect of MBP (Osteoclast) (Isolated osteoclast)

MBP suppresses bone resorption



(Means \pm SD, *p<0.05)

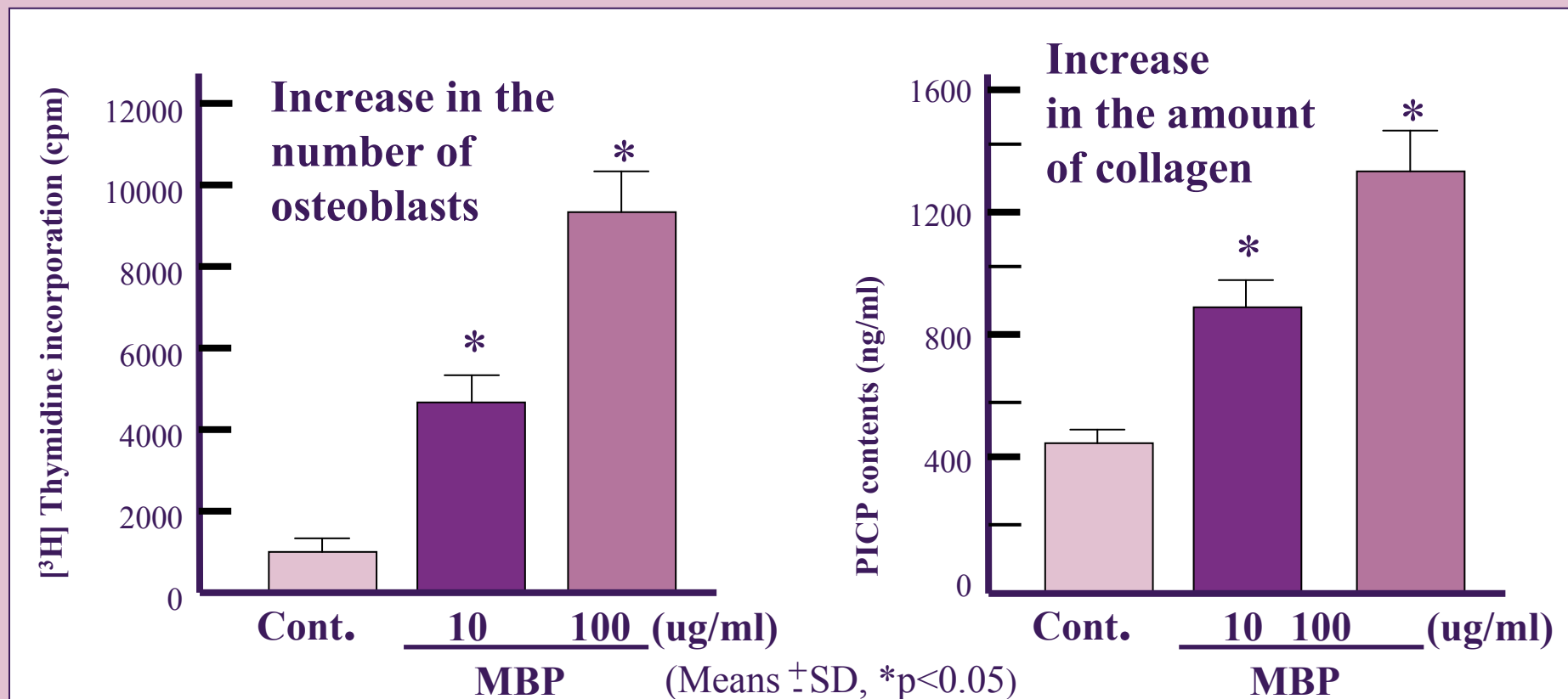
Conclusion:

MBP contains some active components for promoting the growth of osteoblasts.



Collagen Synthesis of Osteoblastic Cells in Cultured Cells

MBP increased PICP (precursor protein of type 1 collagen). Content in MG-63 cells in a dose dependent manner.



Active Components

MBP ion Exchange Chromatography (10-14kDa)

- HMG – like (high mobility group) protein
- Nuclear protein implicated in DNA replication and cellular differentiation specific for osteoblasts
- HMW (high molecular weight) kininogen fragment specific for osteoblasts.

**Yamamura, J et-al. Biochem.
Biophys.Res.Commun.
1999; 261: 113-117**

MBP suppressed areas of pits formed by osteoblasts

Effect of MBP on the Dentine-Resorbing Activity by Preexisting and Newly Formed Osteoclasts Derived from Unfractionated Bone Cells and by Isolated Osteoclasts^a

	Control	MBP ($\mu\text{g/ml}$)		
		1	10	100
Pit area by preexisting osteoclasts, mm^2	1.32 \pm 0.16	1.23 \pm 0.12	0.93 \pm 0.09*	0.43 \pm 0.07*
Pit area by newly formed osteoclasts, mm^2	0.85 \pm 0.12	0.84 \pm 0.11	0.73 \pm 0.09*	0.69 \pm 0.09*
Number of pits by isolated osteoclasts	210 \pm 31	167 \pm 24*	87 \pm 18*	35 \pm 16*

^aValues are mean \pm SD

*Significantly different from the control group ($p < 0.05$)

Active Components of Osteoblast inhibition is different to osteoblast activation

- Molecular Weight 23kDa and 10kDa.
- Cystatin – inhibits cathepsin – a key player in bone resorption. MBP is high in cystatin.

Lerner, U.H et-al. Acta Physiol.Scand. 1997.161:81-92

Absorption via small intestines

- Using everted gut sac to study transport across the small intestines

MBP digested and undigested were both absorbed intact in the small intestines.

There is little or no destruction in the stomach

Conclusion:

Active components of MBP digested in the GIT could still be absorbed or transported and retained its suppressive activity against bone resorption.

Effects of Whey Protein on Calcium and Bone Metabolism in ovariectomized rats. Takada, Y et-al. J. Nutr.Sci.Vitaminol. 1997;43:199-210.

- WP in SD female rats ovariectomized and fed low calcium and phosphorus diets for 4 weeks.
- Breaking force required is higher in WP compared with controls.
- Higher amounts of proline, hydroxyproline, hydroxylysine
- Enhanced collagen synthesis

Conclusion:

WP influences OVX rats by increasing bone proteins and collagen.

Milk Basic Protein enhances the bone strength in ovariectomized rats. Kato, Ken et-al J. Food Biochem. 2000; 24: 467-476

3 Groups

1. Control 20% casein
2. 20% casein + 0.1% MBP
3. 20% casein + 1% MBP

- The bone breaking energy of femur in the MBP group was significantly higher than those in the control group.
- Amount of femoral proline, hydroxyproline and hydroxylysine in the MBP group were significantly higher.

Conclusion:

MBP in whey protein increases the amount of bone collagen and enhances bone strength.

Milk Basic Protein: A Novel Protective Function of Milk Against Osteoporosis. Toba, Y et-al. Bone, 2000; 27: 403-408

BMD of femur was measured by dual energy Xray absorptiometry.

- 17 week study of bone resorption

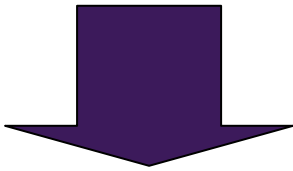
MBP

- Increased serum BGP and PICP (markers of bone formation)
- Decreased serum Deoxypyridinoline (D-Pyr) (markers of bone resorption)

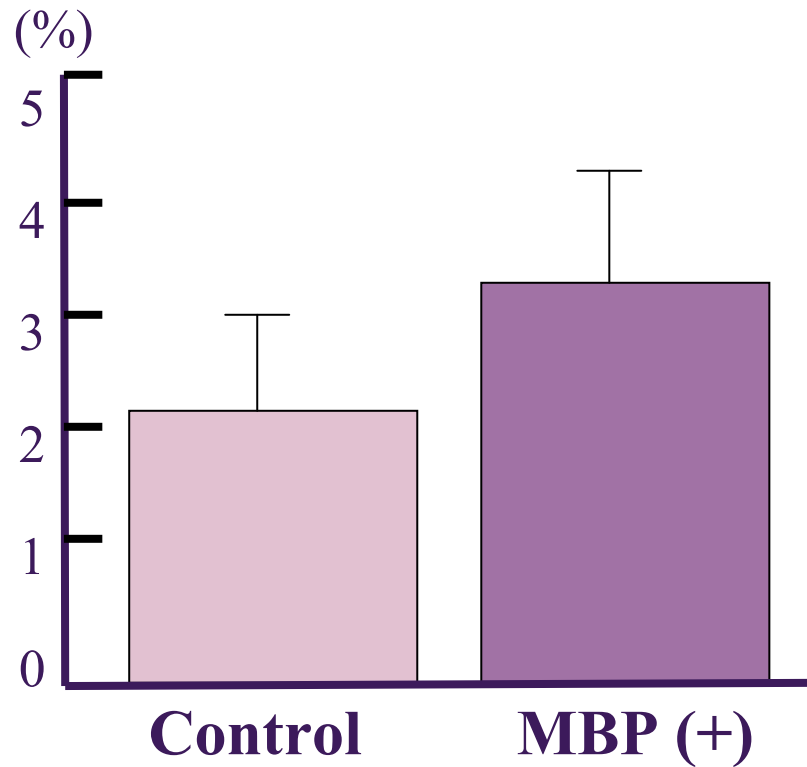
MBP Increases BMD (Calcaneus)

The rate of increase in bone density

MBP



Increase bone density
Promotion of osteogenesis



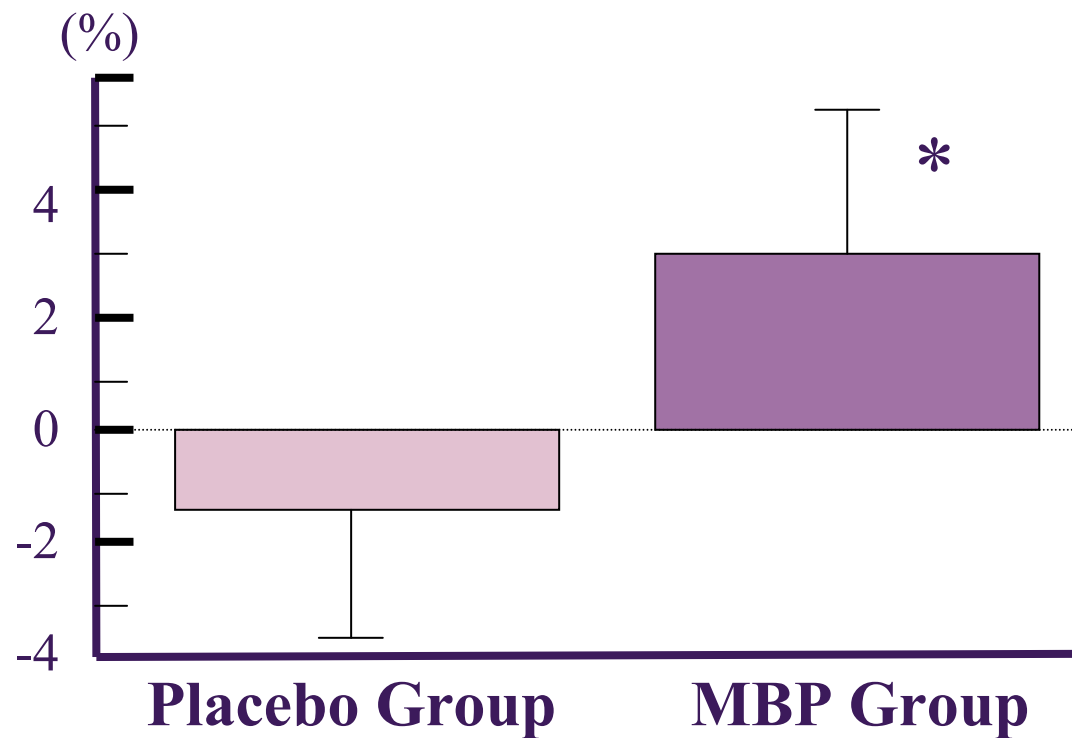


Milk Basic Protein increases Radial Bone Mineral Density in Healthy Adult Women. Yamamura, J et-al. Biosci. Biotechnol. Biochem, 2002; 66: 702-704

- 33 females randomly assigned placebo or MBP (40 mg)
- Radial BMD of each volunteer was measured at the beginning and at 6 months

MBP increases BMD (Radius Distal 1/6)

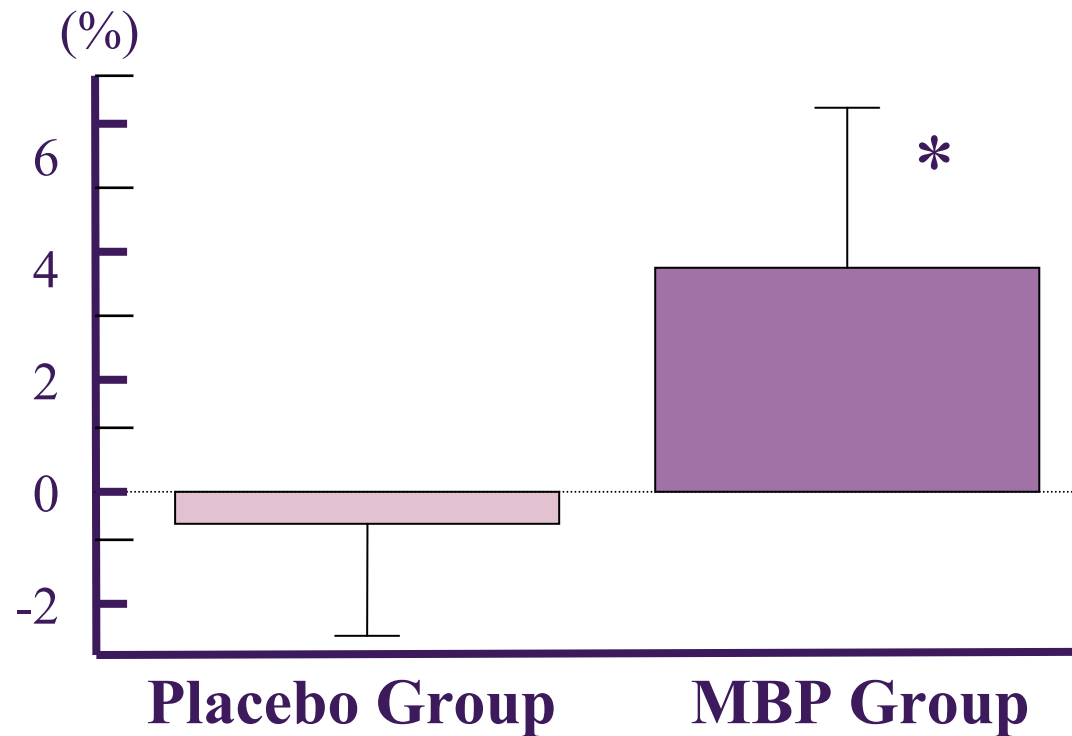
The rate of increase in bone density



(Means \pm SD, *p<0.05)

MBP increases BMD (Radius Distal 1/10)

The rate of increase in bone density



(Means \pm SD, *p<0.05)

Conclusion:

**BMD significantly higher
than the placebo group**



Vitamin K2 Menatetrenone

Essential nutrients such as
vitamins have uses beyond
merely preventing
deficiency

Natural Vitamin K

- K1 (phylloquinone) – plants (leafy green vegetables)
- K2 – synthesized by bacteria (e.g cheese) Natto (fermented soy).
- Family of compounds called MENAQUINONES





Functions

1. Coagulation factors eg II, IV, IX and proteins C and S.
2. Cofactor for microsomal carboxylase enzyme converts glutamyl to γ -carboxyglutamyl residues (GLA) which is Osteocalcin (bone)

Osteocalcin is synthesized by osteoblasts

Osteocalcin has a high affinity to calcium ions and plays a key role in regulatory function in bone mineral maturation. Carboxylated osteocalcin is a sensitive bio marker of bone turnover and Vitamin K status.

3. Calcium Balance – In OVX rats Vitamin K supplementation increased calcium retention.



Warfarin (anti Vitamin K) inhibits
carboxylation of proteins

Results in increased fracture risk.

**There is an inverse relationship
for Vitamin K status and
fracture risk.**


**Booth, S.L. Warfarin and
Fracture Risk. Nutr.Rev.
2000;58:20-29**

Effect of Vitamin K2 on lumbar vertebral bone: Histomorphometric analyses in experimental osteoporotic rats. Xin, F et-al. J. Orthop.Sci. 2001; 6:535-539.

3 Groups		BMD
I	Control	—
II	OVX	↓↓↓↓
III	OVX + Vit K2	↓

Conclusion:

Vitamin K2 had an effect in reducing mineralized bone loss.



Microgravity environment e.g in space flight missions is associated with rapid decreases of carboxylated osteocalcin and increased markers of bone resorption. Calliot, Augusseau, A et-al. Clin.Chemistry. 2000;46:1136-1143

Space flight (21 days and 180 days)

Increased bone resorption markers – C-telopeptide (CTX)
Deoxypyridinoline

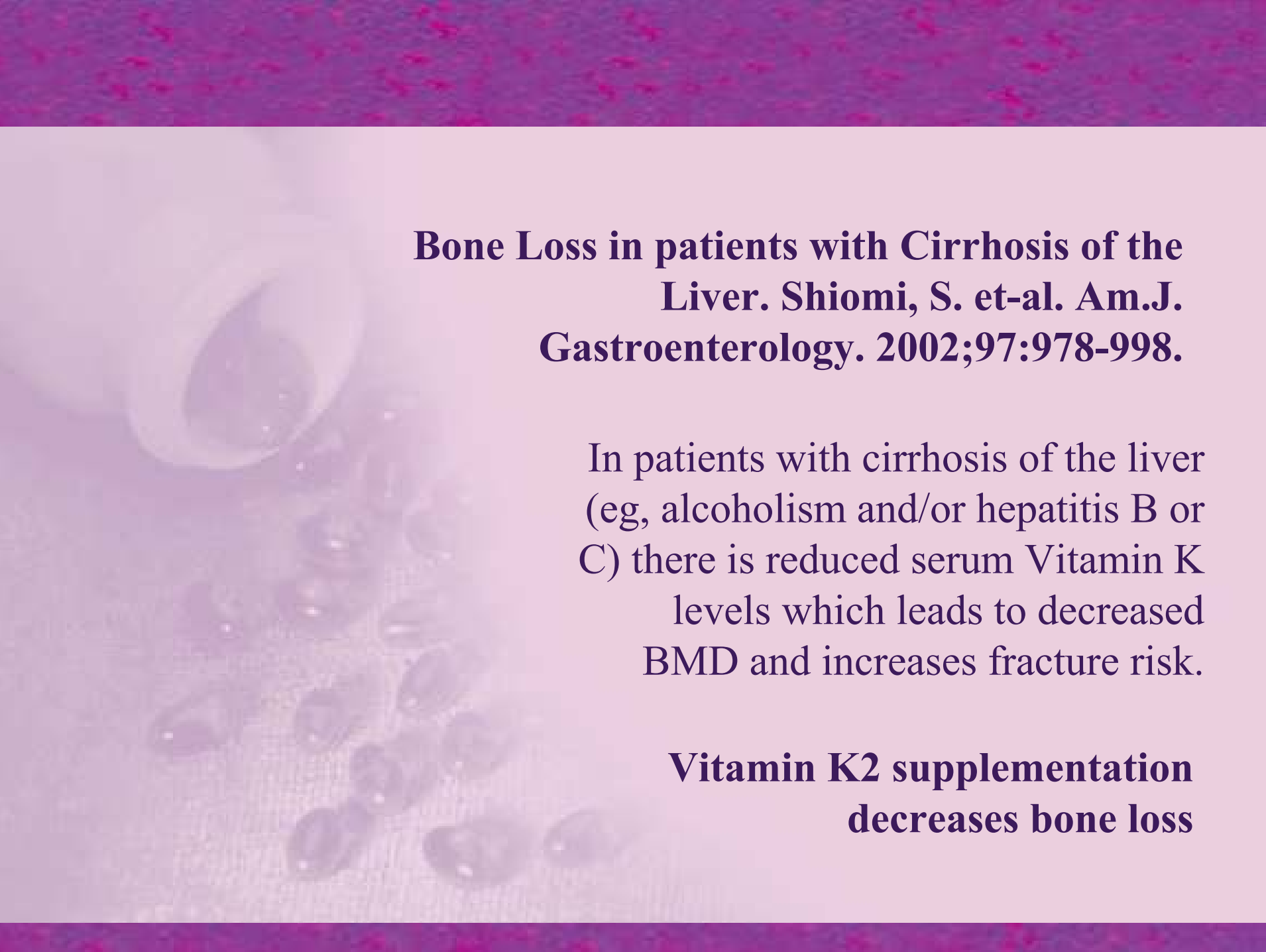
Reduced bone formation markers – Bone Alkaline Phosphatase

Osteocalcin

Type I Procollagen Propeptide (PICP)

N-Telopeptide

Vitamin K2 supplementation increased bone formation and decreased resorption.



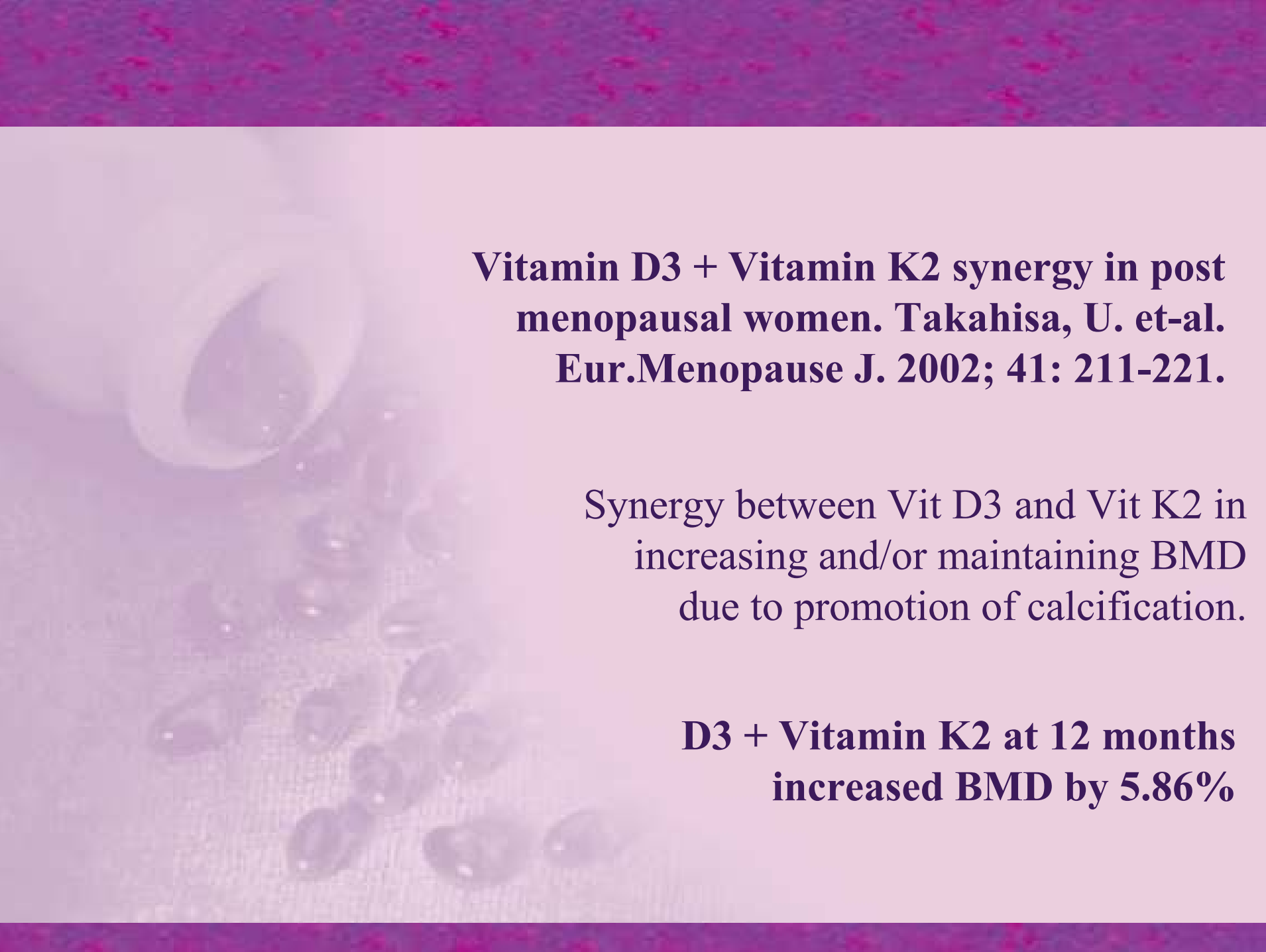
Bone Loss in patients with Cirrhosis of the Liver. Shiomi, S. et-al. Am.J. Gastroenterology. 2002;97:978-998.

In patients with cirrhosis of the liver (eg, alcoholism and/or hepatitis B or C) there is reduced serum Vitamin K levels which leads to decreased BMD and increases fracture risk.

Vitamin K2 supplementation decreases bone loss

Other Uses of Vitamin K2

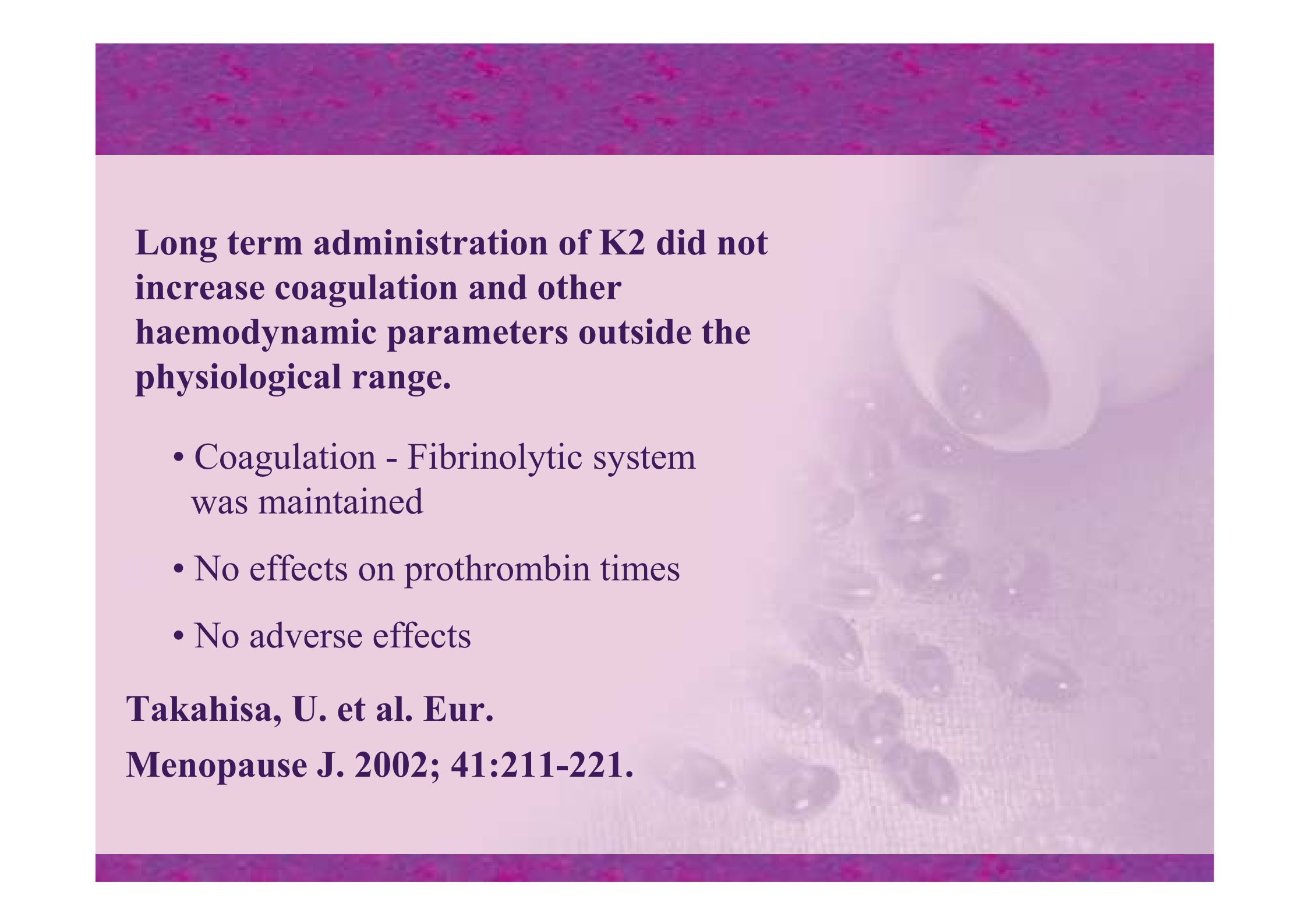
- increases healing of fractures
- decreases incidence of osteoporosis in PD
- reduces incidence of osteoporosis in patients with anorexia nervosa
- protective effect on prednisolone induced bone loss
- vitamin K2 + Bisphosphonates - synergistic effect



**Vitamin D3 + Vitamin K2 synergy in post
menopausal women. Takahisa, U. et-al.
Eur.Menopause J. 2002; 41: 211-221.**

Synergy between Vit D3 and Vit K2 in
increasing and/or maintaining BMD
due to promotion of calcification.

**D3 + Vitamin K2 at 12 months
increased BMD by 5.86%**



Long term administration of K2 did not increase coagulation and other haemodynamic parameters outside the physiological range.

- Coagulation - Fibrinolytic system was maintained
- No effects on prothrombin times
- No adverse effects

Takahisa, U. et al. Eur.

Menopause J. 2002; 41:211-221.




Vitamin K2 effectively prevents fractures and sustains lumbar Bone mineral density in osteoporosis. Shiraki, M et-al. J. Bone Mineral Research. 2000;15:515-521.

241 osteoporotic patients evaluated for 24 months

Vitamin K2 dosage 45mg per day

	Control Group	K2 Group
6m	-1.8 ± 0.6%	1.4 ± 0.7%
12m	-2.4 ± 0.7%	-0.7 ± 0.6%
24m	-3.3 ± 0.8%	-0.5 ± 1%

Vitamin K2 treatment effectively prevents the occurrence of new fractures.



Japanese Fermented Soybean Food as the Major Determinant of the Large Geographic Difference in Circulating Levels of Vitamin K2: Possible implications for hip fracture risk. Kaneki,M. et-al. Nutrition. 2001; 17: 315-321.

- Large Geographic difference in Hip fracture rates in Japan. Eastern Japan (Tokyo) had lower fracture rates than western Japan (Kobe and Osaka).
- Eastern Japan has a higher consumption of Natto compared with Western Japan
- Blood levels of Vitamin K2 higher in Eastern Japan than Western Japan.
- British Women have higher incidence of Hip fracture rates than both East and West Japan and have the lowest Vitamin K2 levels.

Conclusion:

High Natto consumption means high Vitamin K2 blood levels and decreased hip fracture rates.

Vitamin K2 levels are inversely related to hip fracture rates.

Optimal Treatment Protocol for Osteoporosis

Strontium Support (elemental): 680mg/day

Osteo Basic Protein: 40mg/day

Peak K2 (Menatetrenone): 45mg/day



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Thank you