Lifestyle strategies to maximise bone health

Dr Nigel Loveridge & Dr Susan Lanham-New

*Universities of Cambridge and Surrey*
PRESENTATION PLAN

• What is osteoporosis?
• Public health implications of poor bone health?
• Changes in bone mass with ageing
• Importance of exercise to a strong skeleton
• Synergistic effects of calcium and exercise on bone
• Widespread vitamin D insufficiency: implications for health
• Ca and vitamin D supplementation studies for fracture prevention
• Importance of vitamin K to fracture prevention
• Protein, fruit and vegetables and bone
• Other nutrients and lifestyle effects
• Concluding Remarks
DEFINITION OF OSTEOPOROSIS

“A progressive systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue, with consequent increase in bone fragility and susceptibility of fracture.”

NEW WHO FRAX WEBSITE – Just out!


BNF Taskforce on Healthy Ageing, Sainsbury’s Conference Centre, London, Tuesday 13th January 2009
WHY PREVENT FRACTURE?

1:3 women & 1:12 men over 50 yrs - osteoporotic fracture

In UK: 90,000 hip fractures & >100,000? vertebral fractures per yr

Annual cost of osteoporosis
- UK - £1.7 billion
- USA - $17.9 billion
- EU - Euros 13.9 billion

Torgerson et al. (2001). UK Key Advances in Clinical Practice Series
BONE MASS CHANGE WITH AGEING

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ENDOGENOUS vs. EXOGENOUS FACTORS

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EXERCISE AND BONE

Man has the stomach, but not the legs, for Mars

BY JEREMY LAURANCE
Health Editor

THE FIRST person to walk on Mars would break a leg, research published today reveals.

Although there are still several technical problems to be solved before anyone visits the Red Planet, keeping space travellers fit enough during the voyage to take that first step could be one of the trickiest.

The trouble lies with the skeleton and its capacity to withstand a two to three-year journey in zero gravity. When bones are left unused — not bearing any weight — they leak calcium and weaken.

When the travellers to Mars step out of the spacecraft, like stooped elderly women with osteoporosis, they will be at high risk of fractures. A study published in The Lancet of 12 Russian cosmonauts on the space station Mir, found all had suffered bone loss from their legs. In those who spent longest in space — six months — the losses ranged up to 20 per cent.

One cosmonaut had bones that were similar to those of paraplegics. Yet the one who had made the most space "walks" — and had spent longest in space — showed no bone loss at all.

The researchers from St Etienne University in France found the arms of the cosmonauts were unaffected — possibly because they had taken the role of the legs. In space, cosmonauts don't walk — they pull themselves along.

The findings show in-flight exercises to keep the legs in peak condition do not work. And once the cosmonauts returned to Earth, their bones improved but were still significantly weaker six months later than before their mission.

Michael Holick, of Boston University, Massachusetts, says in The Lancet the problem could "substantially affect plans for long distance space travel.

BED REST = bone loss!
CALCIUM & EXERCISE: SYNERGISTIC EFFECTS

2 year exercise intervention with calcium supplementation

Total of 126 POM women studied (mean age 60y)

Strength (loading), fitness or non-exercise control

3 sets of the same 9 exercises, 3x week

Strength group progressively increased their load throughout the study

Significant effect of the strength program at the total hip (0.9 +/- 2.6%, P<0.05) and inter-trochanter site (1.1 +/- 3.0%, P<0.01)

PHYSICAL ACTIVITY & HIGH CA INTAKE

Kerr et al J Bone Miner Res 2001;16:175-181

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Efficiency of vitamin D3 synthesis is dependent on the no. of UVB photons that penetrate into the epidermis.
METABOLISM OF VITAMIN D

7-dehydrocholesterol

UVB

Vitamin D₃ (cholecalciferol)

liver

25(OH)D

kidney

1,25(OH)₂D₃

many tissues

24,25(OH)₂D

calcitriol (calcitriolic acid)

1,24,25(OH)₃D
VITAMIN D INTAKE IN THE UK ELDERLY

Free-living elderly -
97% of participants had intakes below the RNI
8% of participants had low blood levels of 25-OHD

RNI Institutionalised -
99% of participants had intakes below the RNI
37% of participants had low blood levels of 25-OH

HMSO 1998.

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25OHD levels
- <25nmol/l [10ng/ml] – 15.5%
- <40nmol/l [16ng/ml] – 46.6%
- <75nmol/l [30ng/ml] – 87.1%

Hyponnen and Powers AJCN 2007; 85:860-880

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CONSENSUS ON THE NEED FOR INCREASED DIETARY RECOMMENDATIONS
<table>
<thead>
<tr>
<th>Summer</th>
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<th>Winter</th>
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<tr>
<td>June</td>
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<td>December</td>
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<td>Food diary, FFQ &amp; Irish FFQ</td>
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<td>Food diary, FFQ &amp; Irish FFQ</td>
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<td>Grip strength</td>
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<td>Urine sample</td>
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<td>Urine sample</td>
<td>Urine sample</td>
<td>DXA &amp; BUA</td>
<td>Urine sample</td>
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<tr>
<td>Skinfold thickness</td>
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Four Data Collection Points, 223 Caucasian & 70 Asian women

**SPRING 2008 REPEATED**

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25OHD LEVELS FOR OPTIMUM HEALTH

Bischoff-Ferrari et al AJCN 2006

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PREVENTION OF FRACTURE IN THE ELDERLY

Figure 1. Cumulative Probability of Hip Fracture and Other Nonvertebral Fracture in the Placebo Group (□—□) and the Group Treated with Vitamin D₃ and Calcium (●—●), Estimated by the Life-Table Method and Based on the Length of Time to the First Fracture.

COCHRANE VITAMIN D REVIEW - TWO MAIN CONCLUSIONS

(1) Frail older people confined to institutions may sustain fewer hip and other non-vertebral fractures if given Ca and vitamin D

(2) Effectiveness of vitamin D alone is unclear
Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial

Grant et al Lancet 2005; 365:1621-1628

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UK FUNDED CA / VITAMIN D SUPPLEMENTATION TRIALS

Study interpretation: two limiting factors

Compliance with medication – declined to 63% after 2 years.

25OHD measured in small sample (n=60; 1.1% of population)

As low as 45% when non-responders to the Q about compliance were included

Sambrook P. Lancet 2005
Fracture Prevention With Vitamin D Supplementation
A Meta-analysis of Randomized Controlled Trials

Heike A. Bischoff-Ferrari, MD, MPH
Walter C. Willett, DrPH
John B. Wong, MD
Edward Giovannucci, ScD
Thomas Dietrich, MPH
Bess Dawson-Hughes, MD

Fractures contribute significantly to morbidity and mortality of older persons. Hip fractures increase exponentially with age so that by the ninth decade of life, an estimated 1 in every 3 women and 1 in every 6 men will have sustained a hip fracture. With the aging of the population, the number of hip fractures is expected to increase. The role and dose of oral vitamin D supplementation in nonvertebral fracture prevention have not been well established.

Objective To estimate the effectiveness of vitamin D supplementation in preventing hip and nonvertebral fractures in older persons.


Study Selection Only double-blind RCTs of oral vitamin D supplementation (cholecalciferol, ergocalciferol) with or without calcium supplementation vs calcium supplementation or placebo in older persons (≥60 years) that examined hip or nonvertebral fractures were included.

Data Extraction Independent extraction of articles by 2 authors using predefined data fields including study title, authors, year
ETHNIC GROUPS AT RISK FROM VITAMIN D DEFICIENCY

Joint Surrey/Jeddah Study: results in 212 veiled Saudi Arabian women:

Average 25OHD – 8.2ng/ml

Only 1 woman above 12ng/ml

It boosts brittle bones, stops heart attacks — and even tackles dementia. No wonder vitamin K is being hailed as a natural wonder-drug.
Is vitamin K special to bones?

Susan A Lanham-New [QUALS] QUO Nutritional Sciences Division, Faculty of Health and Medical Sciences, University of Surrey, Guildford
Martin J Shearer [QUALS] QUO Consultant Clinical Scientist and Honorary Senior Lecturer, Centre for Haemostasis and Thrombosis, St Thomas’ Hospital, London

Throughout life, the skeleton requires optimum development and maintenance of its integrity to prevent fracture. Bones break because the loads placed upon them exceed the ability of the bone to absorb the energy involved.1 The pathogenesis of osteoporosis is multifactorial. Both the development of peak bone mass and the rate of bone loss are determined by key endogenous and exogenous factors, of which nutrition is key.2

We are constantly striving to identify new and exciting nutrients that may have a role in the maintenance of bone health, although, realistically, there are always many more questions than answers. However, one exciting area of research is vitamin K.3,4 There is solid evidence that, mechanistically, vitamin K has a role in bone health.5 And a healthy diet of green and leafy vegetables is an effective way to secure adequate vitamin K intake.6

Presence of vitamin K in food
A dietary factor that prevented bleeding in chicks was first described in 1929 by the Danish biochemist Henrik Dam. By 1935, Dam had shown that bleeding disorders could be prevented by a fat-soluble substance present in a variety of foods. Similarly, Henry J Knowland in the USA had shown...
VITAMIN K

Dietary-derived coagulation factor – first described in Denmark by Dam and Schonheyder.

Dam 1935: Bleeding disorder in chickens – corrected by feeding a variety of foods – most effectively lucerne (alfalfa) or putrid fish mean

Dam termed the factor – Koagulation-vitamin

Dam together with a number of Swiss chemists, isolated the newest fat soluble vitamin (K) in 1939.
VITAMIN K - CHEMISTRY

Vitamin K exists in two forms: K1 & K2

Both forms have 2-methylnaphthoquinone
Rings with side chains at position three.

K1: phytol side chain – occurs only in plants
K2: family of compounds known as menaquinones, whose side chain consists of a number of isoprene units varying from 1-14 (MK1-MK-14)
K2 is synthesised by bacteria, some of which occur naturally in animals.
Established role for vitamin K is a cofactor specific to the formation of Gla residues
At least 3 vitamin K dependent proteins present in bone and cartilage: osteocalcin, matrix Gla protein (MGP) and protein S

OC: small 49-AA produced by osteoblasts during bone matrix formation. One of the most abundant non-collagenous proteins in bone.

OC synthesis is regulated by 1,25 OHD: hence vitamin D is critical to vitamin K: KEY POINT

MGP: found in cartilage and bone. Synthesis again stimulated by 1,25 OHD.
INFLUENCE OF VITAMIN K ON BONE HEALTH

Low concentrations of circulating vitamin K in patients with hip fracture

Concentration of circulating under-carboxylated osteocalcin associated with age, BMD & fracture risk

Vitamin K supplementation decreases bone loss and Ca excretion
VITAMIN K AND FRACTURE PREVENTION

Vitamin K and the Prevention of Fractures
Systematic Review and Meta-analysis of Randomized Controlled Trials
Sarah Cohney, Miss, Joy Adamson, PhD, Yoon Lee, BM, FRCGP; Martin J. Sharp, PhD, MB, FRCP, FRCR; Siew En Goh, BM, FRCR; David J. Torgerson, MD

Background: Observational and some experimental data suggest that low intakes of vitamin K may be associated with an increased risk of fractures.

Objective: To assess whether vitamin K (phytonadione and menadione) supplementation can reduce bone loss and prevent fractures.

Data Sources: The searches included the following electronic databases: MEDLINE (1966 to June 2005), EMBASE (1980 to June 2005), the Cochrane Library (issue 2, 2007), the ISI Web of Science (1945 to June 2005), the National Research Register (up to the present), Current Controlled Trials, and the Medical Research Council Research Register.

Study Selection: Randomized controlled trials that gave participants oral phytonadione and menadione supplements for longer than 6 months were included in this review.

Data Extraction: Four authors extracted data on changes in bone density and type of fracture. All articles were double-oriented and double-data extracted.

Data Synthesis: Thirteen trials were identified with data on bone loss, and 7 reported fracture data. All studies that showed an advantage of supplementation and menadione were included in the analysis. All trials that reported fracture results were Japanese and used menadione. Pooling the 7 trials with fracture data as meta-analysis, we found a relative risk ratio of 3.89 (95% confidence interval 1.51-9.87) for vertebral fracture, an OR of 2.37 (95% CI, 1.06-5.29) for hip fractures, and an OR of 0.19 (95% CI, 0.11-0.33) for all osteoporotic fractures.

Conclusions: This systematic review suggests that supplementation with phytonadione and menadione—infant bone loss, in the case of the latter, there is strong effect on incisor fractures among Japanese patients.

Arch Intern Med. 2006;166:1320-1327
### Odds Ratio for Vitamin K and Verterbral Fracture Prevention

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio (95% CI)</th>
<th>% Weight</th>
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<tbody>
<tr>
<td>Sasaki 2005</td>
<td>0.35 (0.02, 6.00)</td>
<td>2.9</td>
</tr>
<tr>
<td>Shiraki 2000</td>
<td>0.39 (0.20, 0.75)</td>
<td>54.4</td>
</tr>
<tr>
<td>Iwamoto 2001</td>
<td>0.32 (0.07, 1.46)</td>
<td>10.4</td>
</tr>
<tr>
<td>Ishida 2004</td>
<td>0.47 (0.20, 1.10)</td>
<td>32.4</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>0.40 (0.25, 0.65)</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Cockrayne, Lanham-New, Shearer, Torgerson
*Arch Int Med* 2006;166:1256-1261:
*Arch Int Med* 2007; 167:94-95

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VITAMIN K & HIP FRACTURE PREVENTION

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<tr>
<td>Sato 1998</td>
<td>0.36 (0.02, 5.90)</td>
<td>6.4</td>
</tr>
<tr>
<td>Shiraki 2000</td>
<td>0.26 (0.03, 2.55)</td>
<td>9.7</td>
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<tr>
<td>Sato 2002</td>
<td>0.19 (0.05, 0.75)</td>
<td>27.1</td>
</tr>
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<td>Ishida 2004</td>
<td>0.37 (0.02, 5.90)</td>
<td>6.5</td>
</tr>
<tr>
<td>Sato 2005</td>
<td>0.18 (0.07, 0.49)</td>
<td>50.3</td>
</tr>
<tr>
<td>Overall</td>
<td>0.21 (0.10, 0.43)</td>
<td>100.0</td>
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Cockrayne, Lanham-New, Shearer, Torgerson
Arch Int Med 2006;166:1256-1261:
Arch Int Med 2007; 167:94-95

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ROLE OF THE SKELETON IN ACID:BASE BALANCE

Acid etched holes in osteoporotic bone?

Potassium-rich / Bicarbonate-rich foods play a major role in Ca economy and bone health

Lanham-New (J Nutr 2008 [Jan issue])
Rafferty & Heaney (J Nutr 2008 [Jan issue])
ASBMR, Philadelphia, Nutrition Working Group
ASSOCIATION BETWEEN NEAP & BONE MASS IN 994 SCOTTISH WOMEN

With thanks to Professor Tony Sebastian (USA) for elaborate discussions

New SA et al AJCN 2004;79:131-139
2001 Young Investigator Award, 1st IBMS/ECTS Joint Conference, Spain. Bone 2001;28:S94
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Growing support for a positive link between fruit & vegetable consumption on bone health

Evidence from a combination of observational, clinical and a few intervention studies look promising. DASH-sodium trial (Lin, Ginty et al J Nutr 2003;133:3130-3136)

Editorial: Are fruit & vegetables the unexpected (natural) answer to osteoporosis prevention?
Lanham-New AJCN June 2006

RCT trials are urgently required
12 months supplementation in osteopenic population

Jehle S, Zanetti A, Muser J, Hulter HN and Krapf R. Partial neutralization of the acidogenic Western diet with potassium citrate increases bone mass in postmenopausal women with osteopenia.

J Am Soc Nephrol 2006;17(11), 3213-22

24 months supplementation in healthy population:


Am J Clin Nutr 2008 (August)
Intakes of vitamin A >1500 micrograms RE associated with lower BMD/higher fracture risk

Feskanich et al *JAMA* 2002;287:47-54

Not all studies have confirmed this link
Barker et al *ASBMR* 2004 UK FSA-funded study

**BUT:** high doses of pure cod liver oil can provide as much as 1200 micrograms RE of vitamin A in 10ml dose

SACN September 2006
HCY / VITAMIN B/FOLATE LINK TO BONE

Homocysteine levels and the risk of osteoporotic fracture
Van Meurs JBJ., Dhonukshe-Rutten RAM., Pluijm et al

*New England Journal of Medicine 2004;350:2033-2041*

Homocysteine as a predictive factor for hip fracture in older persons.
McClean RR., Jacques PF., Selhub J., et al.

*New England Journal of Medicine 2004;350:2042-2049*
CONCLUDING REMARKS

Public health impact of osteoporosis will be phenomenal

Vitamin D ‘insufficiency’ in the UK population is extensive

Evidence of a positive effect of Ca and vitamin D supplementation on fracture reduction in the frail elderly

Role of other nutrients is key: Vitamin K, fruit & vegetables, potassium, vitamin B complex;

Smoking, alcohol excess, vitamin A excess, high salt, high caffeine, physical inactivity are all detrimental to bone
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Nutrition & Bone Website
http://sbms.surrey.ac.uk/nutritionandbone/