Vitamin K2: Putting Calcium in its Place and Much More
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The Calcium Paradox
- A lack of calcium where it is needed, e.g. osteoporosis and dental cavities
- An excess of calcium where it is not needed, e.g. atherosclerosis, kidney stones, heel spurs...
- Calcium can get into the wrong places in the body, but it is not calcium’s fault

Why do we calcify?
- In vertebrates, all extracellular body fluids are supersaturated with calcium and phosphate, resulting in a tendency for spontaneous calcium phosphate precipitation
- Potent inhibitors of calcium phosphate precipitation are therefore essential for survival, and there are many in the body.
Why don’t we calcify?

• There are at least 17 known vitamin K-dependent proteins, many of these are calcification inhibitors
• Osteocalcin (OC), Matrix Gla Protein (MGP) and Gla Rich Protein (GRP) are all potent decalifiers in soft tissue
• MGP, OC and GRP are small proteins produced by the tissues that need them... but they require vitamin K2 to be activated (= carboxylated)

50% of all heart attack patients have normal cholesterol levels


Coronary artery calcification (CAC)

• A high CAC score on electron beam tomography has been found to be a better predictor of mortality than age
• Sudden death from heart attack is much more highly correlated with calcification of the aorta than cholesterol
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**MGP and coronary artery calcification**

- Matrix Gla-protein (MGP) is the strongest inhibitor of tissue calcification presently known.
- MGP is produced by small muscle cells in the vasculature where – once carboxylated by K2 – it protects against calcification through several mechanisms.

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**MGP and coronary artery calcification**

- In healthy arteries, there is little accumulation of either MGP.
- In calcified atherosclerotic lesions MGP accumulates, probably because of increased expression.
- Elevated levels of calcium trigger MGP expression in vascular smooth muscle cells in vitro.

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**K2 and plaque stability**

- Another K2 dependent protein, Gas6, has been shown to stabilize advanced plaque, preventing rupture and subsequent thrombus formation leading to myocardial infarction.
Vitamin K

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Vitamin K1
- Aka phylloquinone (synthetic = phytonadione)
- Found in chloroplast membrane
- Vitamin K1 forms a bridge between chlorophyll and several iron-sulphur centres, across which electrons travel
- Discovered by German scientists as essential for “koagulation”, it is as a cofactor in the formation of several coagulation factors the liver.

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Vitamin K1
- Unlike other fat-soluble vitamins, the body does not store vitamin K
- However, the vitamin K cycle allows a small amount of vitamin K1 to be recycled many times, minimizing the dietary requirement
- Best dietary source of vitamin K1 is green leafy veggies
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Non-bleeding side effects of long-term Warfarin therapy

1. Osteoporosis
2. Significant increases in tissue calcification in heart valves, aorta, coronary and carotid arteries and other areas in body
   = The Calcium Paradox

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The K vitamins: major misconceptions

- Vitamin K exists primarily in two forms K1 and K2
- Both K vitamins were discovered in the 1930's
- However, three major misconceptions persisted for 60 years
  - K1 and K2 are merely different forms of the same vitamin (wrong)
  - Blood clotting is their only role (really wrong)
  - Deficiency is rare and obvious (also really wrong)

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Vitamin K: beyond coagulation

- Only in 2007 we learned that
  - it is possible to have a clinically-significant vitamin K (K2) deficiency and without a bleeding disorder
  - Deficiency in very widespread

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**Weak conversion of vitamin K<sub>1</sub> to K<sub>2</sub>**

- Herbivores convert K<sub>1</sub> to K<sub>2</sub> efficiently
- Humans only convert between 5% and 25% of absorbed K<sub>1</sub> to K<sub>2</sub>
- Only ~5% of K<sub>1</sub> in food is absorbed vs. 95% of K<sub>2</sub>
- Vitamin K<sub>2</sub> can also be made by gut flora, but this is not a significant contributor to human nutrition


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**Vitamin K<sub>2</sub>: a new essential nutrient**

- Unlike the other fat-soluble nutrients (A, D, E), vitamin K<sub>2</sub> is not stored in the body
- There is no recycling of K<sub>2</sub>, so it must be provided daily. Humans can develop a deficiency of the vitamin in as few as 7 days on a vitamin K<sub>2</sub>-deficient diet.

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**Vitamin K<sub>1</sub> in the diet: what went wrong?**

1. Industrial farming and confined animal feeding
K<sub>1</sub> is found in dairy, egg yolks, organ of animals that feed on GRASS - not grain

2. Eating less fermented food

Menaquinone-4 MK-6 - MK-10
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Trans fat blocks vitamin K activity

- Trans fat contains an unnatural form of vitamin K produced when oils containing K1 are hydrogenated
- Called dihydrophylloquinone, this unnatural form of vitamin K is unable to activate vitamin K2 dependent proteins
- Individuals on diets containing high amounts of trans fats have lower bone mineral density

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Vitamin K2 and heart disease

- “The risk of incident coronary heart disease, all-cause mortality and aortic atherosclerosis was studied in tertiles of energy-adjusted vitamin K intake after adjustment for age, gender, BMI, smoking, diabetes, education, and dietary factors. Vitamin K1 intake was not related to any of the outcomes.”


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Enter Weston A. Price, D.D.S.

- His studies revealed that dental caries and deformed dental arches resulting in crowded, crooked teeth are the result of nutritional deficiencies, not inherited genetic defects
- His work revealed a strong connection between other health problems – even social and learning problems – and diet
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**Effects of gamma-carboxylation**

- K1 Coagulation
- K2 Bone metabolism
  - Vascular repair
  - Calcification inhibition
  - Regulation of cell proliferation
  - Dental health

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**Clinical effects of K2 deficiency/undercarboxylation of Gla proteins**

- Osteoporosis
- Atherosclerosis: calcification of aorta, coronary arteries, etc.
- Dental caries, crowded teeth in offspring
- Varicosities
- Insulin resistance
- Cancer
- Osteophytes
- Kidney stones

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**Vitamin K2 and bone health**

- There are at least three Gla proteins associated with bone tissue, of which osteocalcin is the most abundant and best known
- Only after its carboxylation by K2 is osteocalcin able to attract calcium ions and incorporate them into hydroxyapatite crystals forming the bone matrix
- When vitamin K2 levels are insufficient, osteocalcin remains uncarboxylated and bone mineralization is impaired
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Vitamin K2 and bone health

• K2 also inhibits osteoclast differentiation and induces apoptosis in osteoclasts
• Works with vitamin D3, which upregulates osteocalcin

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Vitamin K2 and bone health

• Supplementing with K2 increases bone density and reduces fracture risk
• Clinical trials have shown that the combination of K2 and vitamin D3 is more effective in preventing bone loss than either nutrient alone

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New K2 clinical trial

• 180 mcg MK-7 daily for three years significantly
  — decreased the age-related decline in BMC and BMD at the lumbar spine and femoral neck
  — improved bone strength
  — decreased the loss in vertebral height in lower thoracic region

New K2 clinical trial

- 1.5 mg (1,500 mcg) of MK-4 daily for 12 months improved bone metabolism and prevent bone forearm loss

Pregnancy induced osteoporosis

Tsuchie H, Miyakoshi N, Hongo M, et al
http://pubmedcentralcanada.ca/pmccc/articles/PMC3410294/
Profiles 4 typical cases that didn't respond to standard treatment until K2 was added

K2 and menopause

- Estrogen is involved in the conversion of vitamin D to its active bone-building form
- When estrogen levels drop osteoclasts (bone breakdown cells) increase their activity
- The decline in estrogen also increase production of IL-6 which stimulates osteoclast production
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**K2 and menopause**

Supplementing with K2 (MK-7) has been shown to compensate for the changes in bone density due to menopause.


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**K2 and varicosities**

- Undercarboxylated MGP is prevalent in varicose veins compared to healthy veins.
- Smooth muscle cells from varicose veins show enhanced matrix mineralization.
- MGP in varicose veins contribute to venous wall remodeling by affecting proliferation and mineralization processes through impaired carboxylation of MGP.

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**K2 and elastin**

- Maintenance of vascular elasticity during a 3-y supplementation period, with a parallel 12% loss of elasticity in the placebo group.
- Antiwrinkle activity!

Vitamin K2 and metabolic syndrome

- Osteocalcin can stimulate insulin expression in cells and Adiponectin, an insulin-sensitizing adipokine, in adipocytes; in vivo osteocalcin can improve glucose tolerance... The skeleton thus exerts an endocrine regulation of sugar homeostasis...”

Vitamin K2 and dental health

- There are three calcified tissues of the teeth: the cementum, the enamel, and the dentin
- Odontoblasts lining the surface of the pulp just beneath the dentin continually produce new dentin material
- Dentin expresses osteocalcin

Vitamin K2 and dental health

- Price used a combination of high-vitamin cod liver oil (source of A&D) and grass-fed butter oil (source of K2) as the cornerstone of his protocol for reversing dental caries
- This protocol not only stopped the progression of tooth decay, but completely reversed it by causing dentin to grow and remineralize, sealing what were once active cavities
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Vitamin K2 and dental health

- Vitamin K2 exists in the second highest concentration in the salivary glands
- Even when rats are fed only K1, nearly all of the vitamin K in their salivary glands exists as K2

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Vitamin K2 and dental health

Price found that adding activator X
1. Caused minerals to move from saliva into bone/tooth
2. Diminished or eliminated the presence of bacteria in the saliva

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Diseases associated with periodontitis

- Diabetes
- Atherosclerosis, CVD, CHD
- Erectile dysfunction
- Leukemia, pancreatic and other cancers
- Rheumatoid arthritis
- Dementia
- Osteoporosis
Vitamin K2 and the brain
• Vitamin K2 is also found in high concentrations in the brain, where it contributes to the production of myelin and other compounds
• The brain contains one of the highest concentrations of vitamin K2 in the body after the pancreas, salivary glands, and the sternum
• Many K2 actions in the brain likely independent of carboxylation

K2 and cognitive function
• Cognition among Alzheimer’s patients, as measured by the Mini Mental Status Exam, was inversely correlated with inactive osteocalcin (ucOC).
• Vitamin K dependent protein Gas6 rescues cortical neurons from amyloid β protein-induced apoptosis

Vitamin K and pediatric health
• Plays a role in infant and childhood growth by preventing the premature calcification of cartilaginous growth zones of bones
• Price’s work indicates that K2 plays a crucial role in the development of strong bones, straight teeth, good facial proportions, wide facial development and a long straight nose
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Vitamin K2 and pediatric health

- A better vitamin K status was associated with more pronounced increase in bone mass in healthy peri-pubertal children
- Vitamin K status is associated with childhood bone mineral content

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Increasing K₂ intake

- The Western diet contains insufficient vitamin K to meet the requirements of extrahepatic tissues, such as bone and the vascular wall
- Virtually all non-supplemented adults showed K₂ deficiency
- With supplementation (or special foods), it is possible to activate all K₂-dependent proteins

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Vitamin K₂: the menaquinones

- K₁
- K₆
- K₇
K₂: the grass-fed vitamin

- Vitamin K1 is directly associated with both chlorophyll and beta-carotene within a single protein complex and plays a direct role in photosynthesis.
- The colour of grass and its rate of growth directly indicate the concentration of vitamin K1.
- Animals grazing on grass will accumulate vitamin K2 (MK-4) in their tissues in direct proportion to vitamin K1 content of their diet.

Natto

- A traditional Japanese food made from soybeans fermented by Bacillus subtilis natto.
- A breakfast food eaten with rice in some (but not all) areas of Japan.
- Excellent source of K₂ in the form of MK-7.

A statistically significant inverse correlation was found between incidence of hip fractures in women and natto consumption in each prefecture throughout Japan.
K\textsubscript{2} supplements

1. MK-4 is a short-chain menaquinone available as a synthetic compound (menatetrenone)
2. MK-7, a long chain menaquinone, is naturally derived from natto fermentation
   Non-soy MK-7 supplements are now entering the market

MK-4 supplements

- The majority of the research been done using synthetic MK-4 at doses of 45 mg (45,000 mcg) per day (typically 15 mg three times daily due to short half-life)
- At least one recent trial has shown benefits of MK-4 in doses of 1.5 mg (1,500 mg)

MK-7 supplements

- MK-7 is highly bioavailable and bioactive: as little as 45 mcg/day is sufficient to activate osteocalcin
- MK-7 has serum half-life of 3 days – enables the body to build up a reserve that can continuously supply vitamin K2 to all tissues
Menaquinone – 4 (MK-4)  |  Menaquinone – 7 (MK-7)
Source          | Synthetic  | Natural (natto)
Recommended dosage | Typically 45 mg (45,000 mcg) New trials: 1.5 mg (1,500 mcg) | 45 - 400 mcg
Dosing frequency | Divided dose: three times daily  | Once daily
Half life in body | A few hours, hence the need for frequent dosing | A few days, days, so a one a day dosing is fine

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**K₂ and oral anticoagulants (OAC)**

- Early reports suggested less than 50 mcg of MK-7 induced more complete carboxylation of osteocalcin without interfering with OAC therapy
- New studies suggest that for some people, as little as 10 mcg K2 can affect clotting.


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**K₂ and OAC in practice**

- Avoiding vitamin K is difficult. This leads to unpredictable fluctuations in INR.
- A better course of action would be to recommend regular intake of vitamin K and titrate warfarin dose accordingly.
- Vitamin K₂ supplementation protects against reduces diet-induced fluctuations in their INR values.
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Interactions between vitamins A, D and K2

- Osteocalcin is responsible for organizing calcium deposition in bones and teeth
- Cells only produce this protein in the presence of both vitamins A and D
- However, osteocalcin will only facilitate the deposition of calcium salts once it has been activated by vitamin K2

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Interactions Between Vitamins A, D and K2

- Vitamin D upregulates the expression of Gla-proteins, whose activation depends on vitamin K2
- Vitamin D thus increases both the demand for vitamin K and the potential for benefit from K-dependent proteins in blood vessels


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Toxicity of fat soluble vitamins

- Adequate Vitamin D protects against vitamin A toxicity
- Adequate vitamin A protects against D toxicity
- “An extreme imbalance between vitamins A and D leads to the synthesis of abnormally high amounts of MGP. If there is enough vitamin K to activate all of the MGP, it will help protect the soft tissues from calcification. If not, soft tissue calcification ensues”

Masterjohn C., Vitamin D toxicity redefined: vitamin K and the molecular mechanism,” Med Hypotheses, 2007; 68(5): 1026-34
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Indications for K2 supplementation

- Osteoporosis
- Atherosclerosis, history of CVD
- Obesity, diabetes, metabolic syndrome
- Varicose veins
- Dental caries
- Prostate cancer
- Viral cirrhosis
- Periodontitis
- Alzheimers
- Renal disease
- In infants, children, pregnant, lactating women
- Improving VO2max
- Cystic fibrosis
- Menopause
- MS
- RA
- Adolescence

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On the horizon: K2 testing

- K2 is not directly detectable in the blood stream
- Measure of K2 levels by measuring K2-dependant proteins and how much of them are carboxylated
- Desphospho-uncarboxylated MGP was found to be predictive of cardiovascular risk and mortality, whereas circulating total ucMGP was associated with the extent of prevalent arterial calcification
- These test should be available to practitioners within a year

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In conclusion

Vitamin K2 deficiency may be the most important and under recognized nutritional deficiency contributing to the major diseases of our day.

This has happened due to industrial farming practice and consumption of processed foods.

A mass movement towards grass-fed animal products and traditional foods is required to restore our intake of all fat soluble vitamins.