THE ROLE OF VITAMIN K2 (MK-7) IN BONE HEALTH

by Trygve Bergeland, PhD
Vice President Science & Product Development
Kappa Bioscience AS
SCIENTIFIC UPDATE - OVERVIEW

**VITAMIN K2**

- Biochemistry
- Physiology & metabolism
- Biomarkers
- Health effects
### History

**Timeline Overview – Discovery and Rediscovery of Vitamin K2**

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1600s</td>
<td>Japanese warriors consumed K2-rich fermented soya beans – natto</td>
</tr>
<tr>
<td>1930s</td>
<td>Dam discovered a fat-soluble substance that reduced bleeding; Doisy determined the chemical structure of vitamin K &amp; succeeded in synthesizing it</td>
</tr>
<tr>
<td>1943</td>
<td>Dam &amp; Doisy shared the Nobel Prize in Medicine for discovery of vitamin K family</td>
</tr>
<tr>
<td>1950s</td>
<td>K2 forms were first identified. Price’s ‘Activator X’ (K2), the missing ingredient for Teeth and bone health</td>
</tr>
<tr>
<td>1960s</td>
<td>K2 as MK4 became an approved drug in Japan</td>
</tr>
<tr>
<td>1970s</td>
<td>Vermeer started scientific work on enzymes &amp; coagulation</td>
</tr>
<tr>
<td>1990s</td>
<td>Motohara et. al. studied the transfer of K2 between mothers and newborns</td>
</tr>
<tr>
<td>2015</td>
<td>Knapen et. al and Kurnatowska et. al. demonstrated K2 effect on reducing cardiovascular risk</td>
</tr>
<tr>
<td>2016</td>
<td>Møller et. al demonstrated that synthetic K2 (K2VITAL®), and natural-fermented K2 are biologically equivalent</td>
</tr>
</tbody>
</table>

**Introduction**

*Medication and vitamin need for Teeth and bone health*

**Vitamin K2**

**Vitamin K1** (Phyloquinone)

**Vitamin K2**

**Vitamin K3** (Menadione)

**Vitamin K4** (Menadione)

**Vitamin K5** (Menadiol)

**Vitamin K6** (MK-6)

**Vitamin K7** (MK-7)

**Vitamin K8** (MK-8 & MK-9)

**Vitamin K9** (MK-10)

**Vitamin K10** (MK-11)

**Vitamin K11** (MK-12)

**Vitamin K12** (MK-13)

**Vitamin K13** (MK-14)

**Vitamin K14** (MK-15)

**Vitamin K15** (MK-16)

**Vitamin K16** (MK-17)

**Vitamin K17** (MK-18)

**Vitamin K18** (MK-19)

**Vitamin K19** (MK-20)

**Vitamin K20** (MK-21)

**Vitamin K21** (MK-22)

**Vitamin K22** (MK-23)

**Vitamin K23** (MK-24)

**Vitamin K24** (MK-25)

**Vitamin K25** (MK-26)

**Vitamin K26** (MK-27)

**Vitamin K27** (MK-28)

**Vitamin K28** (MK-29)

**Vitamin K29** (MK-30)

**Vitamin K30** (MK-31)

**Vitamin K31** (MK-32)

**Vitamin K32** (MK-33)

**Vitamin K33** (MK-34)

**Vitamin K34** (MK-35)

**Vitamin K35** (MK-36)

**Vitamin K36** (MK-37)

**Vitamin K37** (MK-38)

**Vitamin K38** (MK-39)

**Vitamin K39** (MK-40)

**Vitamin K40** (MK-41)

**Vitamin K41** (MK-42)

**Vitamin K42** (MK-43)

**Vitamin K43** (MK-44)

**Vitamin K44** (MK-45)

**Vitamin K45** (MK-46)

**Vitamin K46** (MK-47)

**Vitamin K47** (MK-48)

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**Vitamin K60** (MK-61)

**Vitamin K61** (MK-62)

**Vitamin K62** (MK-63)

**Vitamin K63** (MK-64)

**Vitamin K64** (MK-65)

**Vitamin K65** (MK-66)

**Vitamin K66** (MK-67)

**Vitamin K67** (MK-68)

**Vitamin K68** (MK-69)

**Vitamin K69** (MK-70)

**Vitamin K70** (MK-71)

**Vitamin K71** (MK-72)

**Vitamin K72** (MK-73)

**Vitamin K73** (MK-74)

**Vitamin K74** (MK-75)

**Vitamin K75** (MK-76)

**Vitamin K76** (MK-77)

**Vitamin K77** (MK-78)

**Vitamin K78** (MK-79)

**Vitamin K79** (MK-80)

**Vitamin K80** (MK-81)

**Vitamin K81** (MK-82)

**Vitamin K82** (MK-83)

**Vitamin K83** (MK-84)

**Vitamin K84** (MK-85)

**Vitamin K85** (MK-86)

**Vitamin K86** (MK-87)

**Vitamin K87** (MK-88)

**Vitamin K88** (MK-89)

**Vitamin K89** (MK-90)

**Vitamin K90** (MK-91)

**Vitamin K91** (MK-92)

**Vitamin K92** (MK-93)

**Vitamin K93** (MK-94)

**Vitamin K94** (MK-95)

**Vitamin K95** (MK-96)

**Vitamin K96** (MK-97)

**Vitamin K97** (MK-98)

**Vitamin K98** (MK-99)

**Vitamin K99** (MK-100)

**Vitamin K100** (MK-101)

**Vitamin K101** (MK-102)

**Vitamin K102** (MK-103)

**Vitamin K103** (MK-104)

**Vitamin K104** (MK-105)

**Vitamin K105** (MK-106)

**Vitamin K106** (MK-107)

**Vitamin K107** (MK-108)

**Vitamin K108** (MK-109)
Scientific Attention

PubMed Results Showing a Spike in K2 Publications in the Last Decade
Vitamin K1
Phylloquinone

Vitamin K2 MK-4
Menaquinone-4

Vitamin K2 MK-7
Menaquinone-7
Dietary Sources

Western Diets Are K2 Deficient

Introduction
- Carboxylation (protein activation)
- Vitamin K cycle
- Coagulation factors
- Osteocalcin
- Matrix gla-protein (MGP)
VITAMIN K DEPENDENT MODIFICATIONS OF GLUTAMIC ACID RESIDUES IN PROTHROMBIN
(proton magnetic resonance spectroscopy/ mass spectrometry)

Johan Stenflo*, Per Fernlund*, William Egan † and Peter Roepstorff ‡
OSTEOCALCIN

Only synthesized in osteoblasts

Carboxylation allows calcium binding and mineralization

Mechanical function by binding hydroxyapatite and collagen

ENDOCRINE FUNCTIONS

Pancreas
- Insulin synthesis
- β-cell proliferation

Brain
- Neurotransmitter Production

Muscle
- Insulin sensitivity

Adipose
- Insulin sensitivity
- Adiponectin
- Fat mass

Testes
- Testosterone

Booth et al. 2013, Nature Review

Zoch et al., Bone 2016; 82;42-9
Bone health

Bone Mass

Age

0 10 20 30 40 50 60 70 80

Puberty

Menopause

High dose K needed for growing bones

Adjust high dose K to reduce bone loss
Bone Health

Decreased Levels of Circulation Carboxylated Osteocalcin in Children with Low Energy Fractures; A Pilot Study

Janusz Popko, Michał Karpiński, Sylwia Chojnowska, Katarzyna Maresz, Robert Milewski, Cladimir Badmaev, Leon J. Schurgers

Design
Pilot study

Intervention
No intervention

Participants
- 20 children with confirmed fracture
- 19 children with no fracture
- Aged 5-17 years
- 23 boys
- 16 girls

Nutrients 2018, 10, 734; doi: 10.3390/nu10060734

Undercarboxylated osteocalcin (ucOC) vs. Carboxylated osteocalcin (cOC)

UCR (ucOC/cOC)

Children with bone fracture vs. non-fracture controls

Nutrients 2018, 10, 734; doi: 10.3390/nu10060734
ASSOCIATION BETWEEN OC AND FRACTURES

<table>
<thead>
<tr>
<th>DESIGN</th>
<th>Observational trial</th>
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<tr>
<td>POPULATION</td>
<td>Age of 70 and older</td>
</tr>
<tr>
<td>SAMPLE SIZE</td>
<td>792</td>
</tr>
<tr>
<td>FOLLOW-UP PERIOD</td>
<td>5 years</td>
</tr>
<tr>
<td>MAIN ENDPOINTS</td>
<td>Fractures, carboxylated and total osteocalcin</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex and OC form</th>
<th>Fracture cases</th>
<th>Controls</th>
<th>p*</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>mean (SD)</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOC</td>
<td>21</td>
<td>9.45 (4.76)</td>
<td>280</td>
</tr>
<tr>
<td>COC</td>
<td>21</td>
<td>6.66 (4.22)</td>
<td>279</td>
</tr>
<tr>
<td>COC/TOC</td>
<td>21</td>
<td>0.74 (0.36)</td>
<td>279</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOC</td>
<td>85</td>
<td>13.45 (7.56)</td>
<td>406</td>
</tr>
<tr>
<td>COC</td>
<td>84</td>
<td>9.17 (5.32)</td>
<td>403</td>
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<tr>
<td>COC/TOC</td>
<td>84</td>
<td>0.77 (0.46)</td>
<td>403</td>
</tr>
</tbody>
</table>

* t-Test

Luukinen, J Bone Miner Res 2000; 15(12); 2473-8
**Bone Health**

**Three-Year Low-Dose Menaquinone-7 Supplementation Helps Decrease Bone Loss in Healthy Postmenopausal Women**

M. H. J. Knapen, N. E. Drummen, E. Smit, C. Vermeer, E. Theuwissen

*Osteoporos Int. 2013; 24(9); 2499-507*

**Design**
Double-blinded, randomized, placebo controlled

**Intervention**
180µg/d MK-7 for 3 years

**Participants**
244 healthy postmenopausal women

**Endpoints**
- Carboxylated osteocalcin
- Uncarboxylated osteocalcin
- Bone mineral content
- Bone mineral density
BONE HEALTH

OSTEOCALCIN

Bone health (uncarboxylated osteocalcin) (carboxylated osteocalcin)

BONE MINERAL CONTENT & BONE MINERAL DENSITY

MK-7 Placebo

Knapen et al. 2013
**Bone Health**

**Vitamin K2 (menaquinone-7) Prevents Age-related Deterioration of Trabecular Bone Micro-Architecture at the Tibia in Postmenopausal Women**

Sofie Hertz Rønn, Torben Harsløf, Stehen Bønløkke Pedersen, Bente Lomholt Langdahl

Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus C, Denmark

<table>
<thead>
<tr>
<th>DESIGN</th>
<th>Double-blinded, randomized, placebo controlled</th>
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<tbody>
<tr>
<td>INTERVENTION</td>
<td>375µg/d MK-7 for 12 months</td>
</tr>
<tr>
<td>PARTICIPANTS</td>
<td>148 healthy postmenopausal women</td>
</tr>
<tr>
<td>ENDPOINTS</td>
<td>- Trabecular bone structure</td>
</tr>
<tr>
<td></td>
<td>- Uncarboxylated osteocalcin</td>
</tr>
<tr>
<td></td>
<td>- Bone mineral density</td>
</tr>
</tbody>
</table>

European Journal of Endocrinology (2016) 175, 541-549
CONCLUSION

SUGGESTS THAT MK-7 PRESERVES TRABECULAR BONE STRUCTURE AT THE TIBIA

**Microarchitecture and Bone Density**

Tibia

Suggests that MK-7 preserves trabecular bone structure at the tibia.
### Included trials:

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>Country</th>
<th>Number</th>
<th>OS?</th>
<th>Age</th>
<th>Follow-up</th>
<th>Intervention</th>
<th>Comparison intervention</th>
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<tbody>
<tr>
<td>Shiraki et al.</td>
<td>RCT without details</td>
<td>Japan</td>
<td>121/120</td>
<td>Y</td>
<td>67.2±0.8</td>
<td>24 M</td>
<td>45 mg/day menatetrenone + C</td>
<td>150 mg/day Ca</td>
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<tr>
<td>Iwamoto et al.</td>
<td>RCT without details</td>
<td>Japan</td>
<td>29/21</td>
<td>Y</td>
<td>55–81</td>
<td>24 M</td>
<td>45 mg/day menatetrenone + C</td>
<td>0.75 μg/day VD3</td>
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<tr>
<td>Iwamoto et al.</td>
<td>RCT without details</td>
<td>Japan</td>
<td>24/23</td>
<td>Y</td>
<td>53–78</td>
<td>24 M</td>
<td>45 mg/day menatetrenone</td>
<td>2 g/day Ca</td>
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<td>Ishida et al.</td>
<td>RCT with details</td>
<td>Japan</td>
<td>66/66</td>
<td>Y</td>
<td>50–75</td>
<td>24 M</td>
<td>Menatetrenone 45 mg/d + C</td>
<td>Placebo</td>
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<tr>
<td>Orimo H et al.</td>
<td>RCT without details</td>
<td>Japan</td>
<td>41/39</td>
<td>Y</td>
<td>-72</td>
<td>24 W</td>
<td>90 mg/day menatetrenone</td>
<td>Placebo</td>
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<td>Emaus et al.</td>
<td>RCT with details</td>
<td>Norway</td>
<td>167/167</td>
<td>N</td>
<td>50–60</td>
<td>12 M</td>
<td>360 μg MK-7 + C</td>
<td>Placebo</td>
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<tr>
<td>Binkley et al.</td>
<td>RCT with details</td>
<td>America</td>
<td>129/126</td>
<td>N</td>
<td>~62</td>
<td>12 M</td>
<td>45 mg/day menatetrenone + C</td>
<td>Placebo</td>
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<tr>
<td>Koitaya et al.</td>
<td>RCT with details</td>
<td>Japan</td>
<td>24/24</td>
<td>N</td>
<td>50–65</td>
<td>12 M</td>
<td>1.5 mg/day MK-4</td>
<td>Placebo</td>
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<tr>
<td>Kasukawa et al.</td>
<td>RCT without details</td>
<td>Japan</td>
<td>50/51</td>
<td>Y</td>
<td>&gt;60</td>
<td>12 M</td>
<td>45 mg/day menatetrenone + C</td>
<td>17.5 mg/week risedronate</td>
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<tr>
<td>Kanellakis et al.</td>
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<td>Greece</td>
<td>38/39</td>
<td>N</td>
<td>54–73</td>
<td>12 M</td>
<td>100 μg MK-7 + C</td>
<td>800 mg Ca 10 μg VD3</td>
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<tr>
<td>Moschonis et al.</td>
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<td>Greece</td>
<td>26/24</td>
<td>N</td>
<td>55–65</td>
<td>12 M</td>
<td>100 μg MK-7 + C</td>
<td>800 mg Ca 10 μg VD3</td>
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<tr>
<td>Je et al.</td>
<td>RCT without details</td>
<td>Korea</td>
<td>40/38</td>
<td>N</td>
<td>&gt;60</td>
<td>6 M</td>
<td>45 mg/day menatetrenone + C</td>
<td>400 IU VD3qd 315 mg Ca bid</td>
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<tr>
<td>Shiraki et al.</td>
<td>RCT without details</td>
<td>Japan</td>
<td>60/62</td>
<td>Y</td>
<td>68.6±7.6</td>
<td>6 M</td>
<td>45 mg/day menatetrenone + C</td>
<td>133.8 mg/day Ca</td>
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<td>2193/2185</td>
<td>Y</td>
<td>&gt;50</td>
<td>48 M</td>
<td>45 mg/day menatetrenone + C</td>
<td>Oral Ca</td>
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<tr>
<td>Hirao et al.</td>
<td>RCT without details</td>
<td>Japan</td>
<td>26/22</td>
<td>N</td>
<td>~68</td>
<td>12 M</td>
<td>45 mg/day vitamin K2 + C</td>
<td>5 mg/day alendroate</td>
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<tr>
<td>Knapen et al.</td>
<td>RCT with details</td>
<td>Netherlands</td>
<td>164/161</td>
<td>N</td>
<td>55–75</td>
<td>36 M</td>
<td>45 mg/day menatetrenone</td>
<td>Placebo</td>
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<tr>
<td>Purwosunu et al.</td>
<td>RCT with details</td>
<td>Indonesia</td>
<td>30/33</td>
<td>Y</td>
<td>60–75</td>
<td>48 W</td>
<td>45 mg/day menatetrenone + C</td>
<td>1500 mg Ca</td>
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<td>RCT without details</td>
<td>Japan</td>
<td>43/43</td>
<td>Y</td>
<td>~53.4</td>
<td>24 M</td>
<td>45 mg/day menatetrenone + C</td>
<td>1 μg/day VD3</td>
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<tr>
<td>Knapen et al.</td>
<td>RCT with details</td>
<td>Netherlands</td>
<td>124/120</td>
<td>N</td>
<td>55–65</td>
<td>36 M</td>
<td>180 μg MK-7/day</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

**Does vitamin K2 play a role in the prevention and treatment of osteoporosis for postmenopausal women: A meta-analysis of randomized controlled trials**

Z.-B. Huang, S.-L. Wan, Y.-J. Lu, L. Ning, C. Liu, S.-W. Fan

Osteoporos Int. 2015; 26(3); 1175-86

19 RTC trials, 6759 participants, MK-7 and MK-4
### Conclusion

**Vitamin K2 Plays a Role in the Maintenance and Improvement of Vertebral BMD and the Prevention of Fractures in Postmenopausal Women with Osteoporosis**
INTERACTION WITH OTHER NUTRIENTS

MK-7

Bone calcium content

Stronger bones

Osteocalcin expression in the osteoblasts

Calcium uptake

CALCIUM

VITAMIN D

Stronger bones

Calcium uptake

Bone calcium content

Osteocalcin expression in the osteoblasts
**SUMMARY**

**VITAMIN K2**

- Biomarkers
- Health effects
- Biochemistry
- Physiology & metabolism
THANK YOU

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