

The most important human clinical trials on Vitamin K2

References update



Cardiovascular
Health



Kidney Health



Bone Health





Other (Efficacy,
Dose Finding,
Absorption, etc.)



Weight loss

Beneficial Effects of Long-Term Menaquinone-7 Supplementation on Cardiovascular Health

Year	Responsible party	Number of participants	Subject	Type and dose of Vitamin K
2015	Maastricht University Medical Center	240		 180 mcg Vitamin K2 daily for three years

Purpose

The purpose of the study was to evaluate the possible cardiovascular benefits of long-term daily supplementation of 180 µg MK-7 (as MenaQ7®) in a healthy population. 240 postmenopausal healthy women free from cardiovascular disease and events were randomly included in a placebo-controlled, double-blind, 3-year supplementation study using non-invasive diagnostic methods.



Finding and Publication

Cardiovascular effects were measured using internationally recognized methods (cfPWV, BT, distension, compliance, Young's modulus) for arterial stiffness and elasticity. The women were grouped into low and high arterial stiffness (stiffness index cut-off at 10.8; 50th percentile) at baseline. After 3 years of supplementation, MK-7 had a significant positive effect on cfPWV as well as on arterial elasticity in the group of women having a

stiffness index > 10.8 at baseline, while little effect was recorded for the low stiffness index group (SI < 10.8). The concomitant measures of vitamin K-dependent proteins osteocalcin (OC) and matrix Gla protein (MGP) showed that both proteins were activated during the first year and kept a high activity level throughout the MK-7 supplementation period. Independent from arterial stiffness group supplementation with MK-7 decreased the non-activated MGP by 50%, indicating that MGP activation contributes to the prevention of arterial stiffness and reduced elasticity. Researchers concluded that long-term use of MK-7 improves arterial stiffness in healthy postmenopausal women, especially in women having high arterial stiffness.

Knapen MHJ et al. *Thrombosis and Haemostasis*, 2015; 19:113(5).

Beneficial Effects of Long-Term Menaquinone-7 Supplementation on Bone Health

Year	Responsible party	Number of participants	Subject	Type and dose of Vitamin K
2013	Maastricht University Medical Center	240		 180 mcg Vitamin K2 daily for three years

Purpose

Researchers sought to demonstrate that MK-7 (as MenaQ7®) has a health benefit in apparently healthy postmenopausal women. In a placebo-controlled, randomized, clinical trial, the effect of an MK-7 supplement was monitored during 3 years on bone quantity.



Finding and Publication

The MenaQ7 group significantly increased the circulating active osteocalcin (cOC), a well-established biomarker for bone and vitamin K status. The inactive protein, undercarboxylated osteocalcin (ucOC), in the

MenaQ7 group decreased with 51% +/- 21 % as compared to the placebo group (+4 % +/- 49%). This points to MenaQ7 having a positive bone effect. After 3 years of supplementation, improvements in both bone mineral content (BMC) and bone mineral density (BMD) were statistically significant in the MenaQ7 group. Moreover, bone strength (BS) was statistically improved, demonstrating therapeutic benefits for the MenaQ7 group as compared to the placebo group.

Knapen MHJ et al. *Osteoporos Int*. 2013 Sep;24(9):2499-507.

Yogurt Drink Fortified with Menaquinone-7 Improves Vitamin K Status in a Healthy Population

Year	Responsible party	Number of participants	Subject	Type and dose of Vitamin K
2015	VitaK, Maastricht University	60		 Vitamin K2 as MK-7 Yogurt drink fortified with 28 mcg MK-7, as well as PUFA, vitamins D & C, calcium, and magnesium twice per day for 12 weeks

Purpose

To date, the effects of increased menaquinone intake on markers of vascular health have been investigated using predominantly food supplements. Therefore, researchers sought to study the effects of a menaquinone-fortified yogurt drink (as MenaQ7[®] Vitamin K2 as MK-7) on vitamin K status and markers of vascular health in healthy men and postmenopausal women.



1.94 ng/ml. In accordance, intake of the fortified yogurt drink improved vitamin K status, as measured by significant decreases in uncarboxylated osteocalcin and desphospho-uncarboxylated matrix Gla protein. In summary, consumption of a yogurt drink fortified with low doses of among others MK-7 for 3 months significantly improved vitamin K status in a healthy population, contributing to improved cardiovascular health.

Finding and Publication

Results showed MK-7 was efficiently absorbed from the fortified yogurt drink. Levels of circulating MK-7 were significantly increased from 0.28 to

Knapen MHJ, et al. *J Nutr Sci.* 2015; 4:e35.

Vitamin K Effectively Increases K Status Via Enriched Yogurt and Soft Gel Capsule

Year	Responsible party	Number of participants	Subject	Type and dose of Vitamin K
2016	VitaK, Maastricht University	40		 Vitamin K2 as MK-7 Yogurt enriched with MK-7, vitamins D3 and C, magnesium, n-3 poly unsaturated fatty acids (n-3 PUFA) and fish oil; yogurt fortified with MK-7 only; and MK-7 soft gel capsules

Purpose



The same researchers from the previous human intervention study compared the fasting plasma concentrations of MK-7 from (a) yogurt enriched with MK-7, vitamins D3 and C, magnesium, n-3 poly unsaturated fatty acids (n-3 PUFA) and fish oil (yogurt Kplus), (b) yogurt fortified with MK-7 only (yogurt K) and (c) soft gel capsules containing only MK-7 for 42 days in healthy men and postmenopausal women between 45 and 65 years of age. The MK-7 in the yogurts and the capsules was MenaQ7[®] from NattoPharma ASA.

Finding and Publication

Circulating MK-7, 25-hydroxy vitamin D (25(OH)D) and markers for vitamin K status [uncarboxylated osteocalcin (ucOC) and matrix Gla-protein (dp-ucMGP)] were assessed. The increase in plasma MK-7 with the yogurt Kplus product was more pronounced than the increase in MK-7 with the capsules. However, circulating dp-ucMGP and ucOC were significantly lowered after consumption of both the yogurt products and the MK-7 capsules, reflecting vitamin K status improvement from both delivery methods.

Knapen MHJ et al. *Euro J Clin Nutr* (2016), 1–6.

Vitamin K-Induced Effects on Body Fat and Weight

Year	Responsible party	Number of participants	Subject	Type and dose of Vitamin K
2017	VitaK, Maastricht University	214		 180 mcg Vitamin K2 daily for three years

Purpose

Vitamin K status has been linked to fat and glucose metabolism by several authors, but whether high vitamin K intake influences body weight or composition has remained unclear. To that end, researchers tested the hypothesis that increased vitamin K intake decreases body fat or fat distribution in a randomized, placebo-controlled, human intervention trial of 214 healthy postmenopausal women over 3 years. Participants either received 180 mcg of Vitamin K2 as MK-7 (as MenaQ7®) daily or a placebo.



Finding and Publication

In the total cohort, MK-7 supplementation increased circulating carboxylated osteocalcin (cOC), but had no effect on body composition. In those with an above-median response in OC carboxylation ('good responders'), MK-7 treat-

ment resulted in a significant increase in total and human molecular weight adiponectin and a decrease in abdominal fat mass and in the estimated visceral adipose tissue area compared with the placebo group and the poor responders. The fact that changes in body composition measures or markers for fat or glucose metabolism were not associated with changes in uncarboxylated OC (ucOC) does not support the assumption that ucOC stimulates fat metabolism in humans. Instead, high vitamin K2 intake may support reducing body weight, abdominal and visceral fat, notably in subjects showing a strong increase in cOC.

[Knapen MHJ et al. Euro J Clin Nutr. \(2017\), 1-6.](#)

Vitamin K2 Supplementation and Arterial Stiffness Among Renal Transplant Recipients

Year	Responsible party	Number of participants	Subject	Type and dose of Vitamin K
2017	Lebanese American University School of Medicine, Byblos, Lebanon	60		 Menaquinone-7 at 360 mcg/day for 8 weeks

Purpose



This single-arm, single-center clinical trial evaluated if there is an association between vitamin K2 as MK-7 supplementation (as MenaQ7®) and the change in both subclinical vitamin K status and indices of arterial stiffness among 60 renal transplant recipients with stable graft function. Arterial stiffness was measured using carotid-femoral pulse wave velocity (cfPWV). Subclinical vitamin K deficiency was defined as plasma concentration of dephospho-uncarboxylated Matrix Gla Protein (dp-uc-MGP) > 500 pmol/L.

Finding and Publication

The results showed that 8 weeks of MK-7 supplementation (360 mcg/day as MenaQ7®) was associated with significant improvement in arterial stiffness and 24-hour peripheral and central pressures. The mean reduction in cfPWV was 1.4 m/s, which was well beyond the reduction of 1 m/s recommended for a clinically relevant vascular effect. The main conclusion was that, among renal transplant recipients with stable graft function, MK-7 supplementation was associated with improvement in subclinical K deficiency and arterial stiffness.

[Mansour AG et al. J Am Soc Hypertens. 2017 Jul 13. Pii: S1933-1711\(17\)30255-3.](#)

Pharmacokinetics of Menaquinone-7 (Vitamin K2) in Healthy Volunteers

Year	Responsible party	Number of participants	Subject	Type and dose of Vitamin K
2014	VitaK Maastricht University	121		 Participants received either capsules (180 mcg or 360 mcg) or tablets (75 mcg or 90 mcg), and different MK-7 carrier materials (sunflower oil, casein, or Arabic gum) in 4 independent human intervention studies with healthy volunteers.

Purpose

Because of the widespread use of MK-7 containing supplements, researchers measured MK-7 absorption following a single intake from oil-based capsules and powder-based tablets in four independent human intervention studies with healthy volunteers.



Finding and Publication

The absorption (time-to-peak) of MK-7 from tablets was slower than from capsules, 6 h as compared to 2 h–4 h, respectively. The researchers further found a dose-response relationship for MK-7 at 24 h after the single-dose intakes (at group level). As compared to baseline, circulating MK-7

levels were still elevated at 24 h after intake, confirming the relatively long half-life of MK-7. The different MK-7 carrier materials showed similar 24 h-absorption profiles, indicating that the carrier was not influencing MK-7 absorption. The researchers concluded that the studies demonstrated on a group level that the bioavailability (24h absorption) of MK-7 was similar for capsules and tablets, and also for the different MK-7 carriers. MK-7 absorption from the various formulations showed high intra- and inter-individual differences.

Knapen MHJ et al. *J Clin Trials* (2014) 4: 160

Vitamin K Status in Healthy Volunteers Using Vitamin K2 Supplementation

Year	Responsible party	Number of participants	Subject	Type and dose of Vitamin K
2013	VitaK Maastricht University	42 children, 68 adults		 Children were supplemented with menaquinone-7 (45 mcg MK-7 per day for 8 weeks). Adults were supplemented with three different MK-7 tablets (90 mcg per day for 7 weeks).

Purpose

The first aim of this study was to measure circulating ucOC and dp-ucMGP levels across age groups to establish the tissue-specific vitamin K status during human life. The second aim was to study the response to supplements at different states of vitamin K deficiency.



Finding and Publication

The study established the vitamin K status across age groups based on circulating levels of ucOC and dp-ucMGP (i.e. markers for the vitamin K

status of bone and the vasculature, respectively). Accordingly, the study classified healthy children and adults above 40 years as groups with prominent vitamin K deficiency and thus appropriate groups for vitamin K supplementation. The results further showed that more pronounced vitamin K deficiency, reflected by higher baseline values, gave larger responses to MK-7 supplementation.

Theuwissen E et al. *Food & Function*, 2013;5(2):229–34.

High dpucMGP in Hemodialysis Patients: Risk Factors and Response to Vitamin K2

Year	Responsible party	Number of participants	Subject	Type and dose of Vitamin K
2017	Nephrology Dept., Saint-Joseph University, Lebanon	50		 Menaquinone-7 at 360 mcg for 4 weeks

Purpose

The scientific data showed that the vitamin K2 intake in hemodialysis patients is estimated to be 40% lower than in healthy individuals. To that end, researchers in Lebanon assessed if there is a correlation between vitamin K status and vascular calcification score in hemodialysis patients, and if the K2 supplementation will improve extrahepatic vitamin K status in this Eastern Mediterranean populations.



vitamin K deficiency as assessed by high dephospho-uncarboxylated MGP (dp-ucMGP) plasma levels. High dpucMGP level was significantly correlated with high aortic calcification scores and thus can be used as a non-invasive marker for vascular calcifications. The daily administration of 360 mcg of vitamin K2 (as MenaQ7®) decreased dpucMGP by 86% after 4 weeks and it was well tolerated.

Finding and Publication

The main conclusion was that hemodialysis patients have profound

Aoun M. et al. *BMC Nephrology*. 2017;18:191.

Vitamin K2 Supplementation in Haemodialysis Patients: a Randomized Dose-Finding Study

Year	Responsible party	Number of participants	Subject	Type and dose of Vitamin K
2013	Division of Nephrology, OLV Hospital, Aalst, Belgium, VitaK, Maastricht University	200		 menaquinone-7 at varying levels of 360, 720, or 1080 mcg of MK-7 thrice weekly for 8 weeks

Purpose

The aim of the trial was to investigate whether higher doses of MK-7 (as MenaQ7®) supplemented for a longer period of time would result in a more pronounced activation of MGP, thereby helping to set up future clinical intervention studies investigating the effect of MK-7 supplementation on vascular calcification and cardiovascular mortality in a population of chronic hemodialysis patients.



related to a low dietary vitamin K intake. Pharmacological doses of MK-7 dose-dependently reduced dp-uc-MGP. Menaquinone supplementation may be a novel approach to prevent vascular calcification in chronic hemodialysis patients.

Finding and Publication

Chronic hemodialysis patients have high levels of inactive MGP, possibly

Caluwè R et al. *Nephrol. Dial Transplant*. 2014;29: 1385-1390.

Beneficial Effects of Menaquinone-7 on the Cardiovascular Systems of CKD Patients

Year	Responsible party	Number of participants	Subject	Type and dose of Vitamin K
2013	Medical University of Łódź. Department of Nephrology, Hypertension and Kidney Transplantation. Łódź, Poland	240		 Vitamin K2 (MK-7) + Vitamin D cholecalciferol

Purpose

This study estimated the influence of vitamin K2 administration on vessel calcification in 3.- 5. stage CKD patients over 6 months.



Finding and Publication

In this pioneering, prospective randomized human clinical trial in patients with chronic renal disease, the cardiovascular effects of oral administration of vitamin K2 (MenaQ7®) plus vitamin D or vitamin D alone were evaluated. In this 6-month study, the progression of coronary artery calcifica-

tion index (CAC) and common carotid intima media thickness (CCA-IMT) – both markers of calcium deposits in arteries detected with computerized tomography – showed a slower progression of the calcification in the vitamin K2/vitamin D group than in the D-alone group.

Kurnatowska I, et al. *Pol Arch Int Med*. 2015 Jul 15. pii: AOP_15_066.

Effect of Low-Dose Menaquinone-7 Supplements on the Stability of Oral Anticoagulant Treatment

Year	Responsible party	Number of participants	Subject	Type and dose of Vitamin K
2013	Maastricht University Medical Center	18		 Subjects on acenocoumarol, were supplemented with increasing doses of MK-7 (10-20-45 µg/days)

Purpose

The purpose of the study was to determine the posology for the interference of supplemental MK-7 with vitamin K antagonists (VKA) therapy.


Finding and Publication

The results presented in this study confirm that the much higher antidotal potency of MK-7 compared to K1 extends to even very low doses of MK-7. MK-7 supplementation at doses as low as 10 µg (lower than usual retail dose of

45 µg) significantly influenced anticoagulation sensitivity in some individuals. Hence, patients using VKA as oral anticoagulant medicines should not take MK-7 supplements without consulting their hematologist.

Theuwissen E et al. *J Thromb Haemost*. 2013;11(6):1085-92.

The Efficacy of Vitamin K2 and Calcitriol Combination on Thalassemic Osteopathy

Year	Responsible party	Number of participants	Subject	Type and dose of Vitamin K
2013	Pediatrics, Division of Pediatric Hematology and Oncology Erciyes University, Kayseri, Turkey	20		MenaQ7 Vitamin K2 as MK-7 50mcg (menaquinone-7) and vitamin D (5mcg calcitriol).

Purpose

This prospective monocentric pilot study investigated the effects of a dietary supplement with vitamin K2 (50mcg menaquinone-7) and vitamin D (5mcg calcitriol) on the patients with Thalassemic Osteopathy (TOSP).


instead of drugs is an augmented physiological intake and seems a beneficial alternative for the treatment of TOSP.

Finding and Publication

Although the natural course of TOSP is worsening, or at least stabilizing, this pilot study demonstrated that a combination of vitamin K2 and calcitriol clearly had a positive effect on the bone mineral density of the children with TM during a 1-year period. Supplementation of menaquinone-7

Ozdemir MA et al. *J Pediatr Hematol Oncol.* 2013; 35(8):623-7.

Dose-Finding and Safety Study for Vitamin K2 in Human Volunteers

Year	Responsible party	Number of participants	Subject	Type and dose of Vitamin K
2012	Maastricht University Medical Center	42		MenaQ7 Vitamin K2 as MK-7 10 - 360 mcg Vitamin K2 for 3 months daily

Purpose

The primary objective of this double-blind, randomized, intervention study was to establish the optimal dose of MK-7 (as MenaQ7®) for the carboxylation of the vitamin K-dependent proteins osteocalcin (OC) in bone and matrix-Gla protein (MGP) in the vessel wall, and the effects on thrombin generation (TG) as an indicator of safety. The optimal dose was the concentration at which OC and MGP are > 90% in the active (carboxylated) form.



proteins. Moreover, no adverse effects on thrombin generation were observed. Given the fact that, in Western society, typical total vitamin K intake amounts to 100-150 mcg/d – and that the MK-7 was given on top of a regular diet – this is remarkably low and demonstrates the high potency of this vitamin. In conclusion, vitamin K2 in the form of MK-7 is safe with respect to the hemostatic system, and results in measurable changes in circulating ucOC and ucMGP, which should be beneficial for bone and cardiovascular system health.

Finding and Publication

The results showed that extra MK-7 intake at nutritional doses around the RDI improved the carboxylation of the extra-hepatic vitamin K-dependent

Theuwissen E et al. *Br J Nutr.* 2012; 28;108(6):1017-24.

Vitamin K2 Supplementation to Activate Matrix Gla Protein (MGP) as Endogenous Inhibitor of Vascular Calcification in Hemodialysis Patients

Year	Responsible party	Number of participants	Subject	Type and dose of Vitamin K
2012	RWTH Aachen University	53		 45 mcg, 135 mcg, or 360 mcg of Vitamin K2 daily over 6 weeks

Purpose

Investigate whether daily vitamin K2 (MK-7 as MenaQ7®) supplementation improves the bioactivity of vitamin K-dependent proteins in hemodialysis patients as assessed by circulating desphospho-uncarboxylated MGP (dp-ucMGP), uncarboxylated osteocalcin (ucOC), and noncarboxylated prothrombin (ucFII; PIVKA-II).



dose- and time-dependent decrease in circulating dp-uc MGP, ucOC, and PIVKA-II levels. The best efficacy was seen with the highest dose of vitamin K2 (360 mcg/d), where response rate in the reduction in dp-uc MGP levels was 93%. In summary, the study showed evidence of a functional vitamin K deficiency in hemodialysis patients, which can be treated effectively with vitamin K2 (MK-7) supplementation.

Finding and Publication

This study confirms that most hemodialysis patients have a functional vitamin K deficiency. However, vitamin K2 supplementation induced a

Westenfeld R et al. *Am J Kidney Dis.* 2012;59(2):186-95.

The Effect of Vitamin K Supplementation on Osteocalcin Carboxylation in Healthy Children

Year	Responsible party	Number of participants	Subject	Type and dose of Vitamin K
2009	UMC Utrecht	55		 45 mcg Vitamin K2

Purpose


The objective of the study was to examine the effect of a vitamin K-containing food supplement (MK-7) on osteocalcin carboxylation in healthy children between 6 and 10 years of age in the Netherlands.

Finding and Publication

These findings demonstrate that in healthy, prepubertal children, modest supplementation with MK-7 (as MenaQ7®) increases circulating concentrations of MK-7 and increases osteocalcin carboxylation.

van Summeren MJ et al. *Br J Nutr.* 2009; 102(8):1171-8.

Changes in Parameters of Bone Metabolism in Postmenopausal Women Following a 12-Month Intervention Period Using Dairy Products Enriched with Calcium, Vitamin D, and Phylloquinone (Vitamin K1) or Menaquinone-7 (Vitamin K2): The Postmenopausal Health Study II

Year	Responsible party	Number of participants	Subject	Type and dose of Vitamin K
2012	Department of Nutrition and Dietetics, Harokopio University, Athens, Greece	219		800 mg of calcium and 10 mcg of vitamin D3 and 100 mcg of either phylloquinone (CaDK1) or menaquinone-7 (CaDK2)

Purpose

The objective of the study was to examine the effect of dairy products enriched with calcium, vitamin D3, and phylloquinone (vitamin K1) or menaquinone-7 (vitamin K2) on parameters of bone metabolism in postmenopausal women following a 12-month intervention.


mass indices for the two vitamin K-supplemented groups, mainly reflected in the suppression of serum levels of bone remodeling indices and in the more positive changes in lumbar spine BMD for these two study groups.

Finding and Publication

The study revealed more favorable changes in bone metabolism and bone

Kanellakis S et al. *Calcif Tissue Int.* 2012; 90(4):251-62.

Natto Supplementation to Prevent Loss of Bone Mass in Women Immediately After Menopause

Year	Responsible party	Number of participants	Subject	Type and dose of Vitamin K
2010	University Hospital of North Norway	304		Natto capsules (food suppl.) cont. 360 mcg of Vitamin K2/day

Purpose


The objective of the study was to determine whether Natto supplementation in women immediately after menopause might prevent severe bone loss.

Finding and Publication

MK-7 taken as Natto over 1 year reduced serum levels of ucOC, but did not influence bone loss rates in early menopausal women. Effects on bone loss was not expected as the study time was too short (only 1 year).

Emaus N et al. *Osteoporos Int.* 2010; 21(10):1731-40.

The Effect of Vitamin K2 on Bone Turnover

Year	Responsible party	Number of participants	Subject	Type and dose of Vitamin K
2009	Eisai Inc	100		Menatetrenone (Vitamin K2)

Purpose


To investigate the effect of menatetrenone on bone turnover in postmenopausal patients with osteoporosis.

Finding and Publication

One month of menatetrenone therapy enhanced the secretion and gamma-carboxylation of osteocalcin. Moderate increases of bone resorption and formation markers were observed after 6 months. These changes may contribute to fracture prevention in patients with osteoporosis.

Shiraki M et al. *J Bone Miner Metab.* 2009;27(3):333-40.

Vitamin K2 Supplementation Improves Hip Bone Geometry and Bone Strength Indices in Postmenopausal Women

Year	Responsible party	Number of participants	Subject	Type and dose of Vitamin K
2007	CARIM, University of Maastricht, Maastricht, The Netherlands	325 postmenopausal women		45 mg/day of Vitamin K2 (MK-4, menatetrenone)

Purpose


A randomized, clinical intervention study among 325 postmenopausal women receiving either placebo or 45 mg/day of vitamin K2 (MK-4, menatetrenone) for three years. BMC and hip geometry were assessed by DXA. Bone strength indices were calculated from DXA-BMD, femoral neck width (FNW) and hip axis length (HAL).

Finding and Publication

Vitamin K2 helps maintain bone strength at the site of the femoral neck in postmenopausal women by improving BMC and FNW, whereas it has little effect on DXA-BMD.

Knapen MHJ et al. *Osteoporos Int.* 2007; 18(7):963-72.

Differential Lipoprotein Transport Pathways of K-Vitamins in Healthy Subjects

Year	Responsible party	Number of participants	Subject	Type and dose of Vitamin K
2002	Maastricht University Medical Center	6		2 micromol of each of three K Vitamers (K1, MK-4, and MK-9) dissolved in corn oil

Purpose

The study tested whether differences between K1 and K2 may be explained by the different liposolubility of the various K-vitamins, resulting in their association with different lipoprotein particles.

Finding and Publication

Menaquinones may have a different distribution profile and suggests a relatively large impact of menaquinones on extra-hepatic vitamin K status than generally assumed.

Schurgers LJ et al. *Biochim Biophys Acta*. 2002; 1570(1):27-32.

Key



Cardiovascular Health



Bone Health



Weight loss



Kidney Health



Other (Efficacy, Dose Finding, Absorption, etc.)

Bibliography

These human clinical trials sponsored by NattoPharma have cultivated a greater comprehension of the mechanism and health benefits of Vitamin K2 as MK-7. NattoPharma has trials currently underway and is eager to share these new developments. For now, here is a full bibliography of the important work that has been done thusfar.

- Knapen et al. *Thrombosis and Haemostasis*. 2015;19;113(5).
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