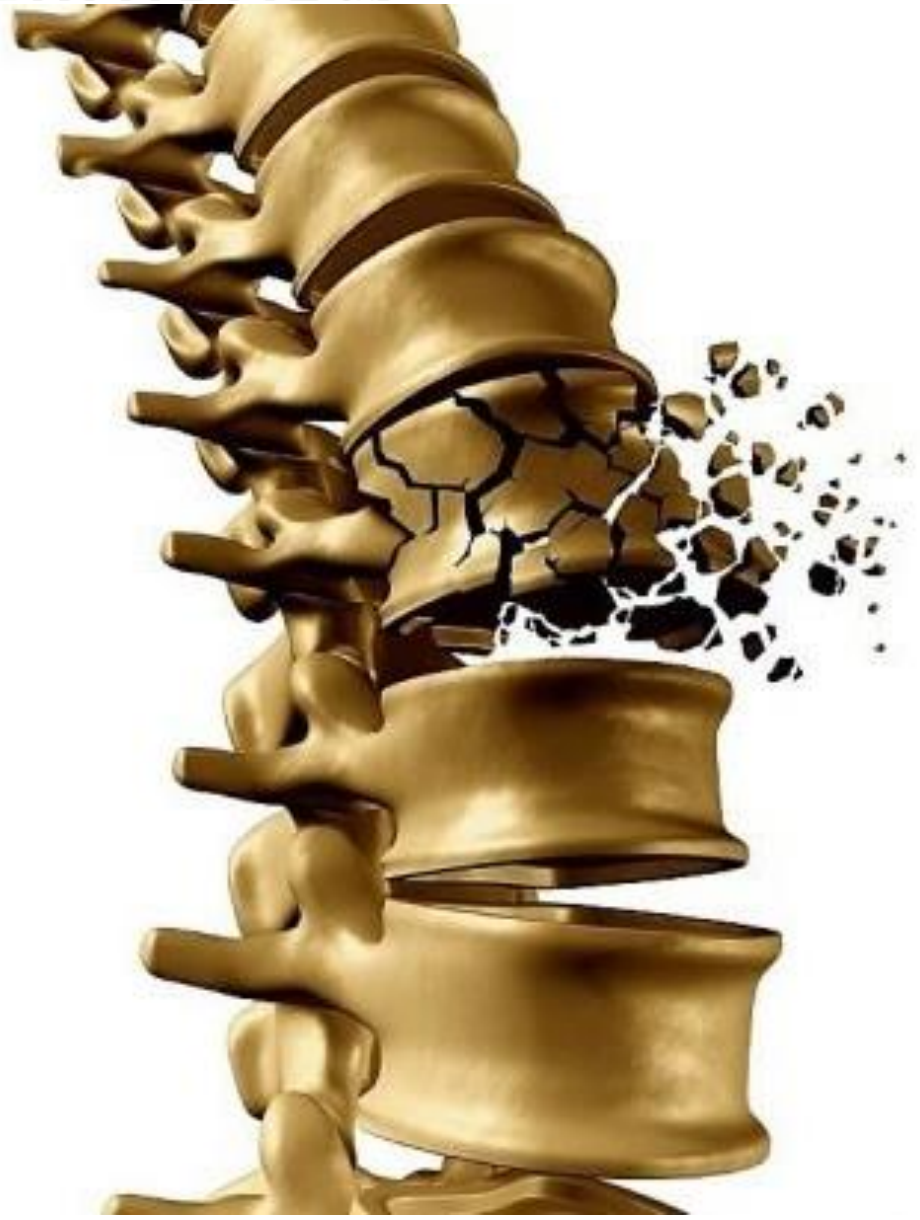
ARMIDAL SRL



Armidik

VITAMINA D3

VITAMINA K2

- ✓ **Migliora l'omeostasi ossea in caso di OSTEOPOROSI**
- ✓ **Riduce l'incidenza di FRATTURE OSSEE**

Armidik

VITAMINA D3

FACILITA l'assorbimento del calcio a livello intestinale e renale.

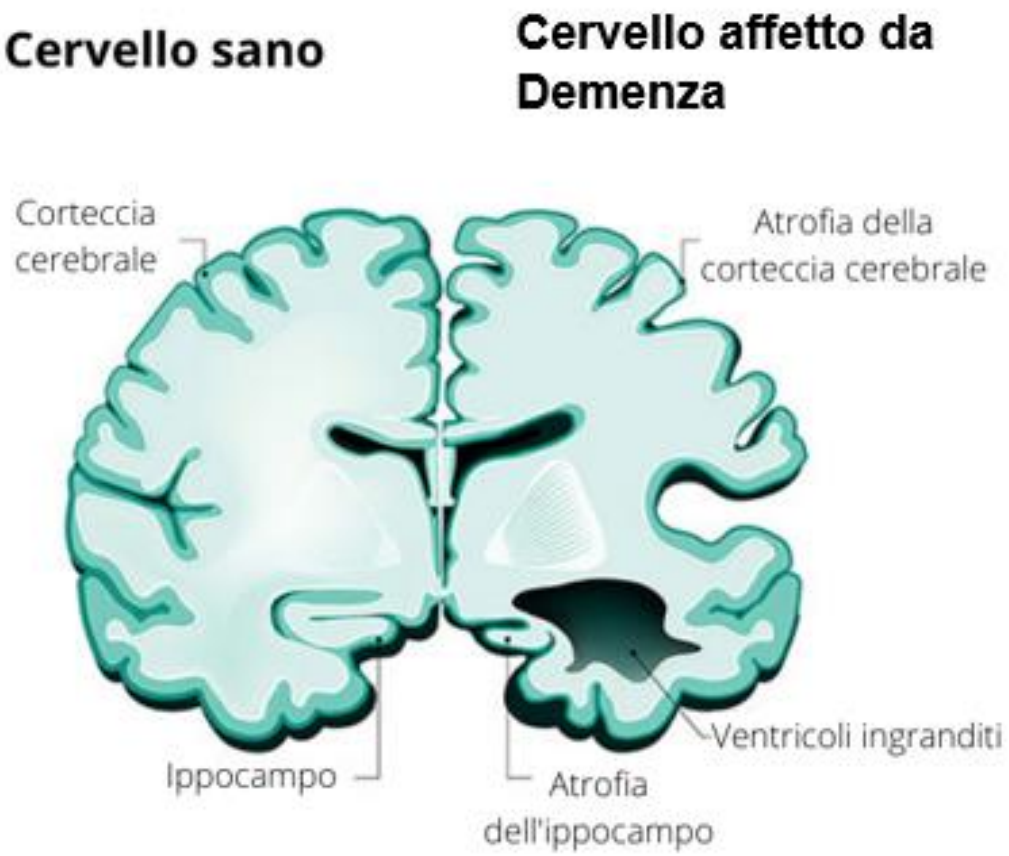
+

VITAMINA K2

MIGLIORA la mineralizzazione ossea

INIBISCE la calcificazione arteriosa

Armidik



- ✓ **Migliora la funzione COGNITIVA**
- ✓ **Riduce la progressione graduale della DEMENZA**

Armidik

- ✓ **IMMUNOSTIMOLANTE**
- ✓ **ANTINFIAMMATORIO**

ASSOCIAZIONE FUNZIONALE

VITAMINA D3 + **VITAMINA K2**

EVITA il potenziale RISCHIO DI IPERCALCEMIA

con conseguente accumulo di CALCIO NELLE ARTERIE

(*CALCIFICAZIONE ARTERIOSA*) e

RIDUCE il rischio di OSTEOPOROSI e FRATTURE OSSEE

IPERVITAMINOSI DI VITAMINA D3

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Prevalence of hypercalcemia related to hypervitaminosis D in clinical practice

C. Pérez-Barrios [a], E. Hernández-Álvarez [a, b], I. Blanco–Navarro [a, b], B. Pérez-Sacristán [b], F. Granado-Lorencio [a, b, *]

L'ipervitaminosi da vitamina D può determinare IPERCALCEMIA

SUMMARY

Background & aims: Recent interest in vitamin D has led to a substantial increase in the use of vitamin D supplements. Vitamin D intoxication may be a concern as hypervitaminosis D can result in irreversible calcification of soft tissues so that it is important to detect early markers of vitamin D intoxication. Our aim was to assess the simultaneous presence of biochemical markers of vitamin D toxicity (i.e. hypervitaminosis D, hypercalcemia) and determine the concentrations of 25-OH-vitamin D at which the risk of hypercalcemia, and thus toxicity, might begin.

Methods: We evaluated retrospectively a 6-year period during which 25.567 samples were assessed for 25-OH-vitamin D status by UHPLC. Hypervitaminosis D was defined at serum 25-OH-vitamin D >160 nmol/L. Serum and urine calcium, phosphorus and iPTH were also recorded, if available. Medical history revision was performed in subjects displaying simultaneously hypervitaminosis D and hypercalcemia.

Results: Overall, hypervitaminosis D was found in 475 samples (1.86%) of which 51 displayed hypercalcemia (11.1%). A total of 382 samples were identified as the first record of hypervitaminosis D and 39 presented hypercalcemia (10.2%), most of them at 25-OH-vitamin D levels between 161 and 375 nmol/L. Only in 15 subjects, hypercalcemia could be directly attributed to vitamin D and serum 25-OH-vitamin D ranged between 164 and 1139 nmol/l. In no case, serum calcium achieved concentrations considered as critical values (>13 mg/dl).

Conclusion: Hypercalcemia due to vitamin D represented <4% of the total hypervitaminosis D detected and <0.1% of the tests performed. However, a highly variable response was observed and most subjects presented hypercalcemia at serum concentrations of 25-OH-vitamin D < 375 nmol/L.

Art: Pérez-Barrios, C., Hernández-Álvarez, E., Blanco–Navarro, I., Pérez-Sacristán, B., & Granado-Lorencio, F. *Prevalence of hypercalcemia related to hypervitaminosis D in clinical practice. Clinical Nutrition, 2016.35(6), 1354–1358..*

VITAMINA K2

La **VITAMINA K** riduce il rischio di **CALCIFICAZIONE VASCOLARE**

Adv Chronic Kidney Dis. 2019;26(6):437-444

ACKD

The Role of Vitamin K in Vascular Calcification

Mario Cozzolino, Maria Fusaro, Paola Ciceri, Lorenzo Gasperoni, and Giuseppe Cianciolo

Vascular calcification (VC) is common in advanced chronic kidney disease (CKD), contributes to cardiovascular disease (CVD), and associates with increased mortality. Major risk factors for VC in CKD are increasing age, dialysis vintage, and positive net calcium-phosphate balance. To date, no specific therapy that prevents progression or facilitates regression of VC beyond careful attention to calcium and phosphate balance exists. Accumulating evidence demonstrates that CKD patients may incur subclinical vitamin K deficiency. This deficiency may be induced by exhaustion of vitamin K due to its high requirement by vitamin K-dependent proteins to inhibit VC. This review analyzes the pathophysiological mechanisms and clinical consequences of vitamin K deficiency with emphasis on its involvement on vascular calcification in CKD and end-stage renal disease and its relationship to the bone-vascular axis.

Keywords: Vascular calcification, Vitamin K, Matrix Gla protein, Chronic kidney disease, Warfarin

CLINICAL SUMMARY

- Vitamin K deficiency associates with vascular calcification.
- CKD patients incur vitamin K deficiency and vascular calcification.
- Vitamin K plays a role in the vascular-bone axis and may prove therapeutic.

VITAMINA K2

Il menachinone-7 (MK-7) è in grado di **ridurre la rigidità delle arterie in donne post-menopausa**

ART: Knapen, M. H. J., Braam, L. A. J. L. M., Drummen, N. E., Bekers, O., Hoeks, A. P. G., & Vermeer, C.. Menaquinone-7 supplementation improves arterial stiffness in healthy postmenopausal women. Thrombosis and Haemostasis, 2015. 113(05), 1135–1144.

Menaquinone-7 supplementation improves arterial stiffness in healthy postmenopausal women

A double-blind randomised clinical trial

Marjo H. J. Knapen[1]; Lavienja A. J. L. M. Braam[1]; Nadja E. Drummen[1]; Otto Bekers[2]; Arnold P. G. Hoeks[3]; Cees Vermeer[1]

[1]VitaK & Cardiovascular Research Institute (CARIM), Maastricht University, The Netherlands; [2]Central Diagnostic Laboratory, University Hospital Maastricht, The Netherlands; [3]Biomedical Engineering, Maastricht University, The Netherlands

Summary

Observational data suggest a link between menaquinone (MK, vitamin K2) intake and cardiovascular (CV) health. However, MK intervention trials with vascular endpoints are lacking. We investigated long-term effects of MK-7 (180 µg MenaQ7/day) supplementation on arterial stiffness in a double-blind, placebo-controlled trial. Healthy postmenopausal women (n=244) received either placebo (n=124) or MK-7 (n=120) for three years. Indices of local carotid stiffness (intima-media thickness IMT, Diameter end-diastole and Distension) were measured by echotracking. Regional aortic stiffness (carotid-femoral and carotid-radial Pulse Wave Velocity, cfPWV and crPWV, respectively) was measured using mechanotransducers. Circulating desphospho-uncarboxylated matrix Gla-protein (dp-ucMGP) as well as acute phase markers Interleukin-6 (IL-6), high-sensitive C-reactive protein (hsCRP), tumour necrosis factor-α (TNF-α) and markers for endothelial dysfunction Vascular Cell Adhesion Molecule (VCAM), E-selectin, and Advanced Glycation Endproducts (AGEs) were measured. At baseline dp-ucMGP was associated with IMT, Diameter, cfPWV and with the mean z-scores of acute phase markers (APMscore) and of markers for endothelial dysfunction (EDFscore). After three year MK-7 supplementation cfPWV and the Stiffness Index β significantly decreased in the total group, whereas distension, compliance, distensibility, Young's Modulus, and the local carotid PWV (cPWV) improved in women having a baseline Stiffness Index β above the median of 10.8. MK-7 decreased dp-ucMGP by 50 % compared to placebo, but did not influence the markers for acute phase and endothelial dysfunction. In conclusion, long-term use of MK-7 supplements improves arterial stiffness in healthy postmenopausal women, especially in women having a high arterial stiffness.

Keywords

Arterial stiffness, carotid intima-media thickness, menaquinone-7, pulse wave velocity, Stiffness Index β

ASSOCIAZIONE FUNZIONALE VIT. D3 + VIT. K2

Hindawi
International Journal of Endocrinology
Volume 2017, Article ID 7454376, 12 pages
https://doi.org/10.1155/2017/7454376

Hindawi

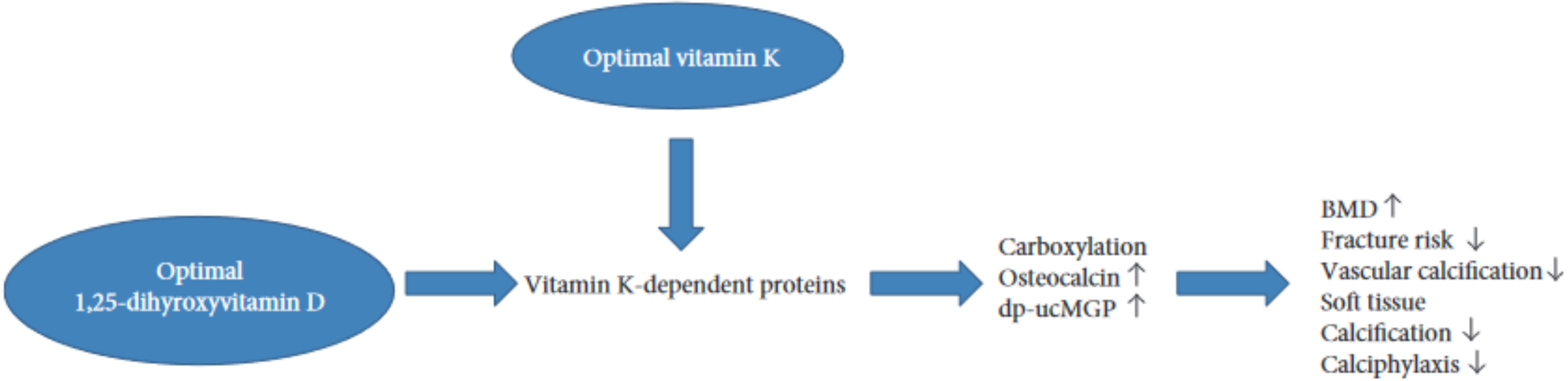
Review Article

The Synergistic Interplay between Vitamins D and K for Bone and Cardiovascular Health: A Narrative Review

Adriana J. van Ballegooijen,[1] Stefan Pilz,[2,3] Andreas Tomaschitz,[4] Martin R. Grübler,[2,5] and Nicolas Verheyen[6]

[1]*Department of Health Sciences, Vrije Universiteit Amsterdam and the Amsterdam Public Health Research Institute, Amsterdam, Netherlands*

Vitamin K is needed for the carboxylation of vitamin K-dependent proteins such as osteocalcin and matrix Gla protein, while vitamin D promotes the production of vitamin K-dependent protein concentrations. These vitamin K-dependent proteins are needed for extrahepatic organs such as the **bone and the vascular system.** This will result in bone mineralization and will inhibit soft tissue calcification, which will ultimately lead to lower risks of **FRACTURES AND CORONARY HEART DISEASE.**



ASSOCIAZIONE FUNZIONALE VIT. D3 + VIT. K2

nutrients

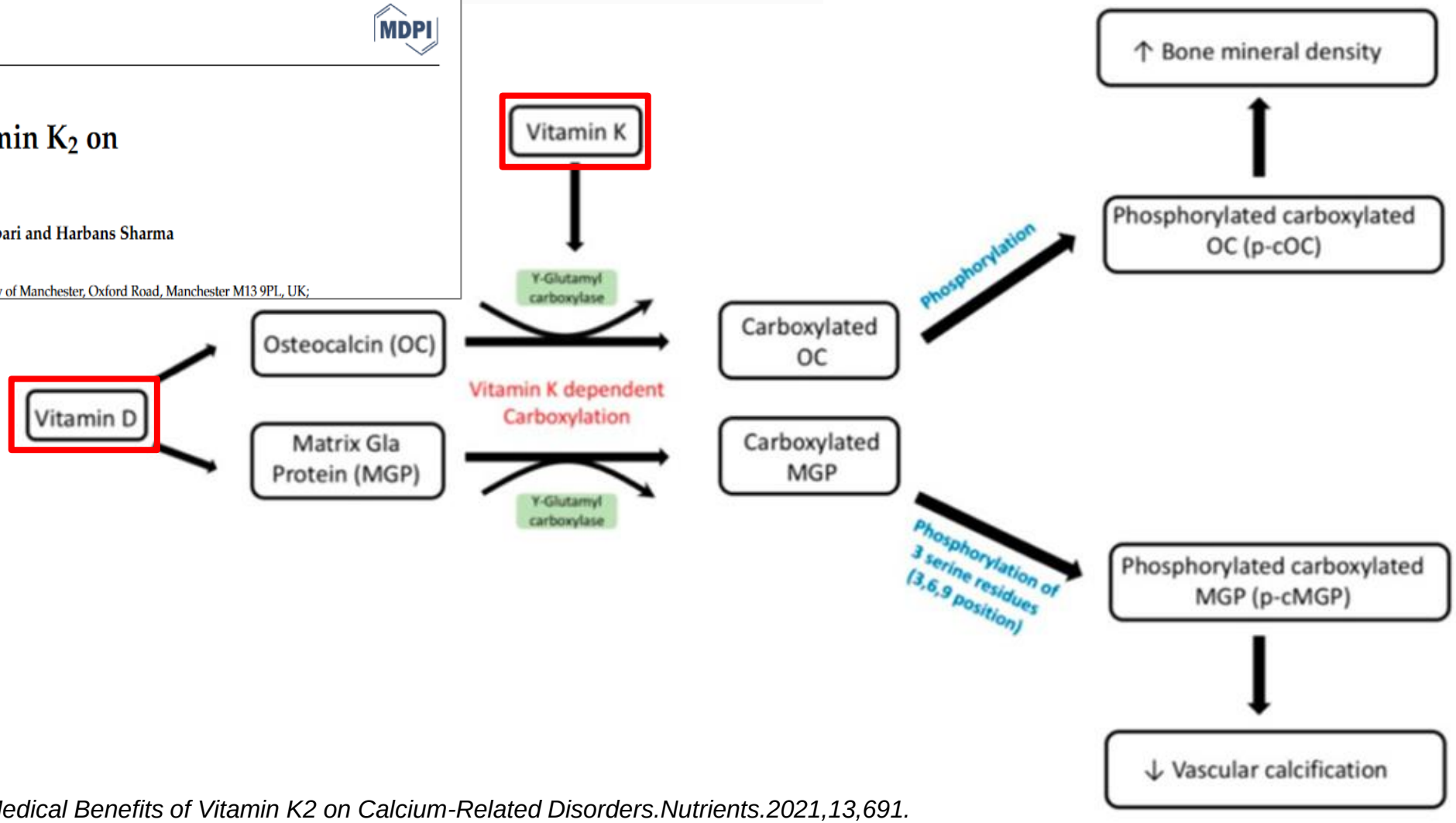
MDPI

Review

The Medical Benefits of Vitamin K_2 on Calcium-Related Disorders

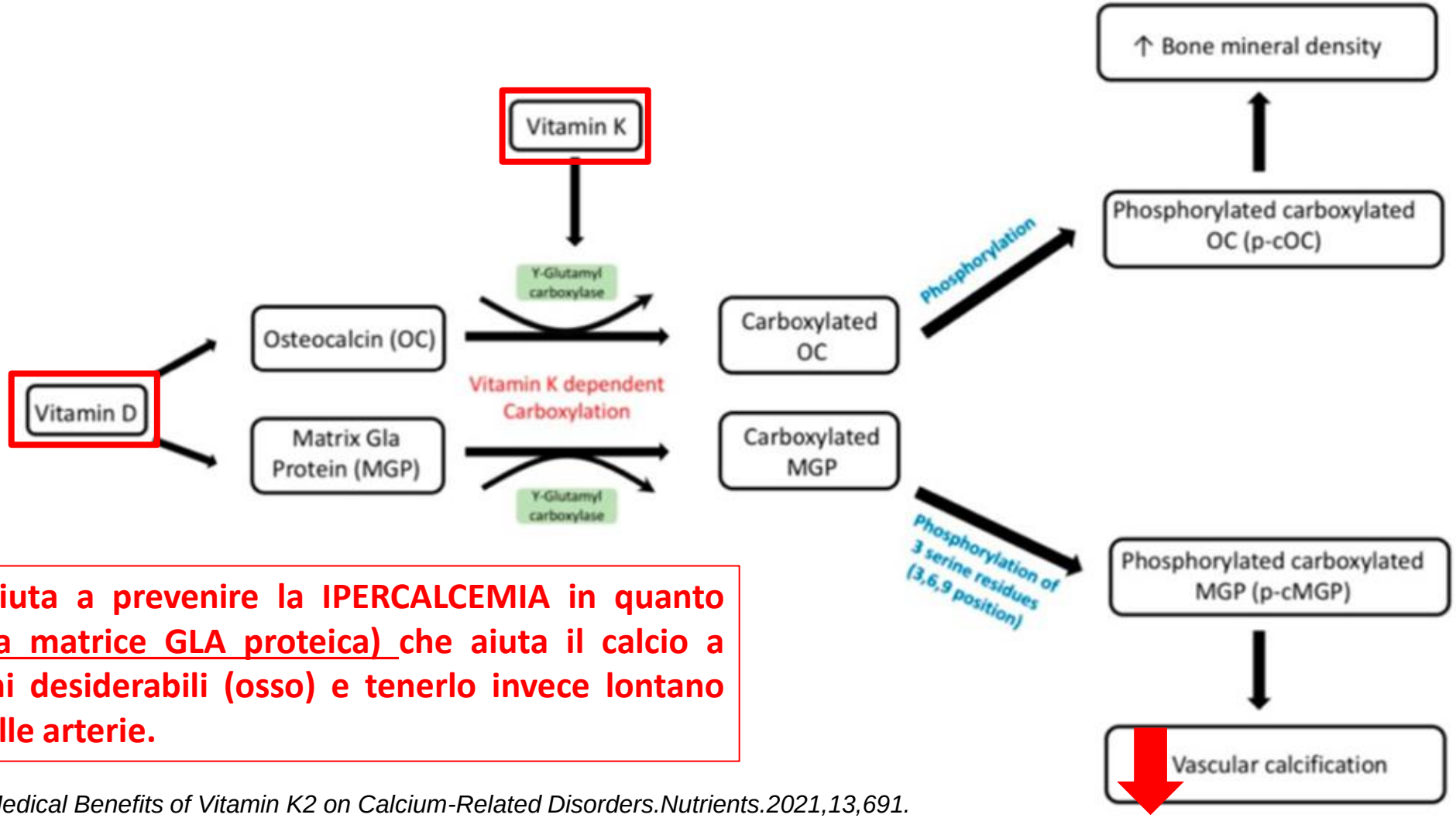
Zeyad Khalil *, Benyamin Alam, Amir Reza Akbari and Harbans Sharma

Medical School, The University of Manchester, Oxford Road, Manchester M13 9PL, UK;



Art: Z. Khalil et al. The Medical Benefits of Vitamin K2 on Calcium-Related Disorders.Nutrients.2021,13,691.

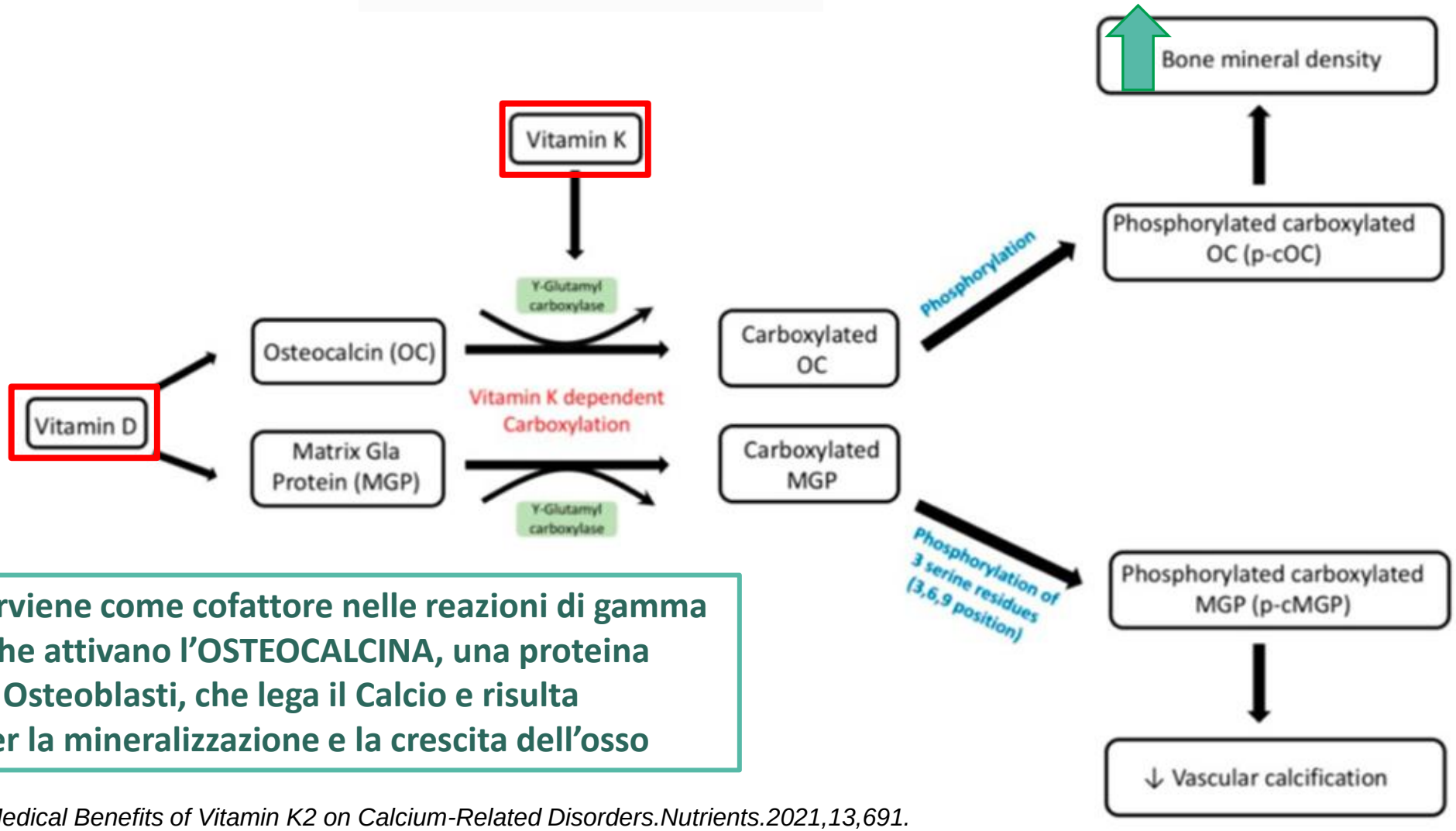
ASSOCIAZIONE FUNZIONALE VIT. D3+K2



La vitamina K aiuta a prevenire la IPERCALCEMIA in quanto attiva il MGP (la matrice GLA proteica) che aiuta il calcio a dirigersi ai luoghi desiderabili (osso) e tenerlo invece lontano dell'accumulo nelle arterie.

Art: Z. Khalil et al. The Medical Benefits of Vitamin K2 on Calcium-Related Disorders.Nutrients.2021,13,691.

ASSOCIAZIONE FUNZIONALE VIT. D3+K2



VITAMINA K interviene come cofattore nelle reazioni di gamma carbossilazione che attivano l'OSTEOCALCINA, una proteina sintetizzata dagli Osteoblasti, che lega il Calcio e risulta indispensabile per la mineralizzazione e la crescita dell'osso

Art: Z. Khalil et al. The Medical Benefits of Vitamin K2 on Calcium-Related Disorders.Nutrients.2021,13,691.

ELEVATISSIMO DOSAGGIO DI VITAMINA D3+K2

1 GOCCIA: pari a 1000 U.I. di VIT D3 (25 mcg) + 5,6 di VIT K2

2 GOCCE: pari a 2000 U.I. di VIT D3 (50 mcg) + 11,25 di VIT K2

Contenuti medi	Per dose 2 gocce	VNR%*
Vitamina D3	50 mcg	1000
Vitamina K2	11.25 mcg	15

(*) Valore nutritivo di riferimento

** U.I. = Unità Internazionali*

COMPOSIZIONE

FACILMENTE DOSABILE IN GOCCE

Contenuti medi	Per dose 2 gocce	VNR%*
Vitamina D3	50 mcg	1000
Vitamina K2	11.25 mcg	15

(*) Valore nutritivo di riferimento

Ingredienti: Olio di girasole (Helianthus annuus L.) semi olio; Olio di Oliva (Olea europaea L.); Vitamina K2 (Menachinone 7); Vitamina D3 (Colecalciferolo).

Cosa sono le UNITA' INTERNAZIONALI?

L'Unità internazionale (U.I.) è ***un'unità di misura della quantità di una sostanza, basata sul suo effetto ovvero sulla sua attività biologica.***

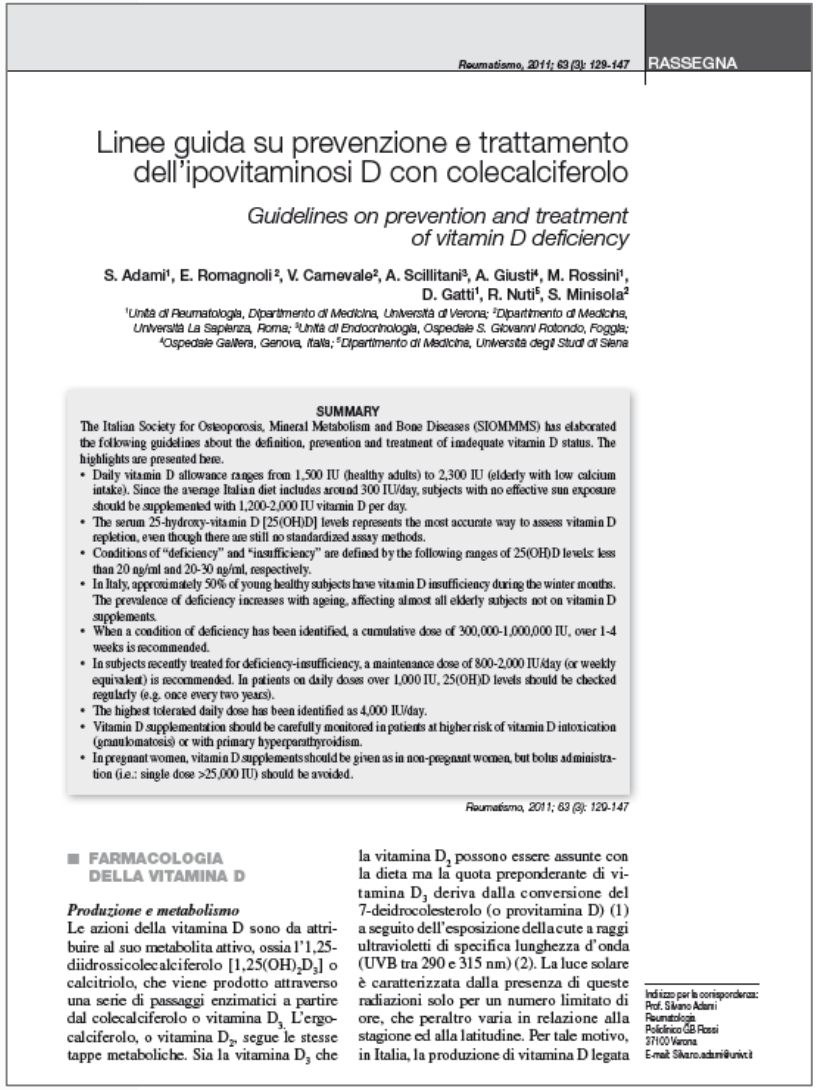
In questo modo, è possibile poter confrontare diverse forme e preparazioni di vitamina D.

1

OSTEOPOROSI

Il problema della carenza di vitamina D **non è esclusivo degli ANZIANI.**

Un recente studio volto a stabilire i valori di normalità dei marker del metabolismo minerale in soggetti giovani e sani ha dimostrato che la carenza di vitamina D interessava il 30 ed il 65% dei soggetti.
Il problema peggiora **nei mesi invernali** anche nei **GIOVANI** ed in particolare nelle **DONNE.**



Reumatismo, 2011; 63 (3): 129-147 RASSEGNA

Linee guida su prevenzione e trattamento dell'ipovitaminosi D con colecalciferolo

Guidelines on prevention and treatment of vitamin D deficiency

S. Adami[1], E. Romagnoli[2], V. Carnevale[2], A. Scillitani[3], A. Giusti[4], M. Rossini[1], D. Gatti[1], R. Nuti[5], S. Minisola[2]

[1]Unità di Reumatologia, Dipartimento di Medicina, Università di Verona; [2]Dipartimento di Medicina, Università La Sapienza, Roma; [3]Unità di Endocrinologia, Ospedale S. Giovanni Rotondo, Foggia; [4]Ospedale Galliera, Genova, Italia; [5]Dipartimento di Medicina, Università degli Studi di Siena

SUMMARY

The Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases (SIOMMMS) has elaborated the following guidelines about the definition, prevention and treatment of inadequate vitamin D status. The highlights are presented here.

- Daily vitamin D allowance ranges from 1,500 IU (healthy adults) to 2,300 IU (elderly with low calcium intake). Since the average Italian diet includes around 300 IU/day, subjects with no effective sun exposure should be supplemented with 1,200-2,000 IU vitamin D per day.
- The serum 25-hydroxy-vitamin D [25(OH)D] levels represents the most accurate way to assess vitamin D repletion, even though there are still no standardized assay methods.
- Conditions of "deficiency" and "insufficiency" are defined by the following ranges of 25(OH)D levels: less than 20 ng/ml and 20-30 ng/ml, respectively.
- In Italy, approximately 50% of young healthy subjects have vitamin D insufficiency during the winter months. The prevalence of deficiency increases with ageing, affecting almost all elderly subjects not on vitamin D supplements.
- When a condition of deficiency has been identified, a cumulative dose of 300,000-1,000,000 IU, over 1-4 weeks is recommended.
- In subjects recently treated for deficiency-insufficiency, a maintenance dose of 800-2,000 IU/day (or weekly equivalent) is recommended. In patients on daily doses over 1,000 IU, 25(OH)D levels should be checked regularly (e.g. once every two years).
- The highest tolerated daily dose has been identified as 4,000 IU/day.
- Vitamin D supplementation should be carefully monitored in patients at higher risk of vitamin D intoxication (granulomatosis) or with primary hyperparathyroidism.
- In pregnant women, vitamin D supplements should be given as in non-pregnant women, but bolus administration (i.e.: single dose >25,000 IU) should be avoided.

Reumatismo, 2011; 63 (3): 129-147

FARMACOLOGIA DELLA VITAMINA D

Produzione e metabolismo

Le azioni della vitamina D sono da attribuire al suo metabolita attivo, ossia l'1,25-diidrossicolecalciferolo [$1,25(OH)_2D_3$] o calcitriolo, che viene prodotto attraverso una serie di passaggi enzimatici a partire dal colecalciferolo o vitamina D_3. L'ergocalciferolo, o vitamina D_2, segue le stesse tappe metaboliche. Sia la vitamina D_3 che la vitamina D_2 possono essere assunte con la dieta ma la quota preponderante di vitamina D_3 deriva dalla conversione del 7-deidrocolesterolo (o provitamina D) (1) a seguito dell'esposizione della cute a raggi ultravioletti di specifica lunghezza d'onda (UVB tra 290 e 315 nm) (2). La luce solare è caratterizzata dalla presenza di queste radiazioni solo per un numero limitato di ore, che peraltro varia in relazione alla stagione ed alla latitudine. Per tale motivo, in Italia, la produzione di vitamina D legata

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OSTEOPOROSI

La carenza di Vit D3 e K2 può verificarsi nel periodo **post-menopausale** causando problemi di **OSTEOPOROSI.**

J Orthop Sci (2000) 5:546–551

Journal of Orthopaedic Science
© The Japanese Orthopaedic Association

Effect of combined administration of vitamin D_3 and vitamin K_2 on bone mineral density of the lumbar spine in postmenopausal women with osteoporosis

JUN IWAMOTO[1], TSUYOSHI TAKEDA[1], and SHOICHI ICHIMURA[2]

[1]Department of Sports Clinic, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
[2]Department of Orthopaedic Surgery, National Defense Medical College, 3-2 Namiki, Tokorozawa, Saitama 359-8513, Japan

Abstract The effect of the combined administration of vitamin D_3 and vitamin K_2 on bone mineral density (BMD) of the lumbar spine was examined in postmenopausal women with osteoporosis. Ninety-two osteoporotic women who were more than 5 years after menopause, aged 55–81 years, were randomly divided into four administration groups: vitamin D_3 (1α hydroxyvitamin D_3, 0.75 μg/day) (D group; $n = 29$), vitamin K_2 (menatetrenone, 45 mg/day) (K group; $n = 22$), vitamin D_3 plus vitamin K_2 (DK group, $n = 21$), and calcium (calcium lactate, 2 g/day) (C group; $n = 20$). BMD of the lumbar spine (L2–L4) was measured by dual energy X-ray absorptiometry at 0, 1, and 2 years after the treatment started. There were no significant differences in age, body mass index, years since menopause, and initial BMD among the four groups. One-way analysis of variance (ANOVA) with repeated measurements showed a significant decrease in BMD in the C group ($P < 0.001$). Two-way ANOVA with repeated measurements showed a significant increase in BMD in the D and K groups compared with that in the C group ($P < 0.05$ and $P < 0.001$, respectively), and a significant increase in BMD in the DK group compared with that in the C, D, and K groups ($P < 0.0001$, $P < 0.05$ and $P < 0.01$, respectively). These findings indicate that combined administration of vitamin D_3 and vitamin K_2, compared with calcium administration, appears to be useful in increasing the BMD of the lumbar spine in postmenopausal women with osteoporosis.

Key words Vitamin D_3 · Vitamin K_2 · Postmenopausal women · Osteoporosis · Bone mineral density (BMD)

Introduction

Osteoporosis is a major public health problem, and is characterized by low bone mass and increased risk of fractures. Marked bone loss is observed, with accelerated bone remodeling after menopause in women. The rate of bone loss in untreated postmenopausal women 3–5 years after menopause is 4.5% per year of spinal trabecular mineral density,[7] and bone loss declines thereafter. Because of the event of menopause, osteoporosis primarily affects postmenopausal women.

When bone mineral density (BMD) decreases below the level of the fracture threshold, osteoporotic fractures, such as vertebral fractures, can actually occur without evidence of a fall.[5] Multiple vertebral fractures not only cause back pain but also produce a round back, which decreases the volume in the thoracic and abdominal cavities, potentially resulting in multiple organ dysfunction. Therefore, even vertebral fractures can be one of the factors in the reduction of life span. Thus, it is important not only to prevent falls but also to prevent loss of vertebral BMD, or to increase vertebral BMD to a level above the fracture threshold to reduce vertebral fractures in people with osteoporosis. One therapeutic approach should focus on preventing loss of vertebral BMD.

In Japan, it is generally recognized that vitamin D_3 or vitamin K_2 treatment can prevent BMD loss of the lumbar spine in postmenopausal women with osteoporosis.[21–23] However, clinically, the effect of combined administration of vitamin D_3 and vitamin K_2 on the BMD of the lumbar spine has not been established. The purpose of the present study was to examine the effect of the combined administration of vitamin D_3 and vitamin K_2 on BMD of the lumbar spine in postmenopausal women with osteoporosis.

Subjects and methods

Subjects

One hundred and eighty-seven women who were more than 5 years after menopause were diagnosed with oste-

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Review

Vitamin K_2 Therapy for Postmenopausal Osteoporosis

Jun Iwamoto

Institute for Integrated Sports Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan; E-Mail: jiwamoto@a8.keio.jp;
Tel.: +81-3-3353-1211; Fax: +81-3-3352-9467

Received: 19 February 2014; in revised form: 4 May 2014 / Accepted: 6 May 2014 / Published: 16 May 2014

Abstract: Vitamin K may play an important role in the prevention of fractures in postmenopausal women with osteoporosis. Menatetrenone is the brand name of a synthetic vitamin K_2 that is chemically identical to menaquinone-4. The present review study aimed to clarify the effect of menatetrenone on the skeleton in postmenopausal women with osteoporosis, by reviewing the results of randomized controlled trials (RCTs) in the literature. RCTs that investigated the effect of menatetrenone on bone mineral density (BMD), measured by dual-energy X-ray absorptiometry and fracture incidence in postmenopausal women with osteoporosis, were identified by a PubMed search for literature published in English. Eight studies met the criteria for RCTs. Small RCTs showed that menatetrenone monotherapy decreased serum undercarboxylated osteocalcin (ucOC) concentrations, modestly increased lumbar spine BMD, and reduced the incidence of fractures (mainly vertebral fracture), and that combined alendronate and menatetrenone therapy enhanced the decrease in serum ucOC concentrations and further increased femoral neck BMD. This review of the literature revealed positive evidence for the effects of menatetrenone monotherapy on fracture incidence in postmenopausal women with osteoporosis. Further studies are required to clarify the efficacy of menatetrenone in combination with bisphosphonates against fractures in postmenopausal women with osteoporosis.

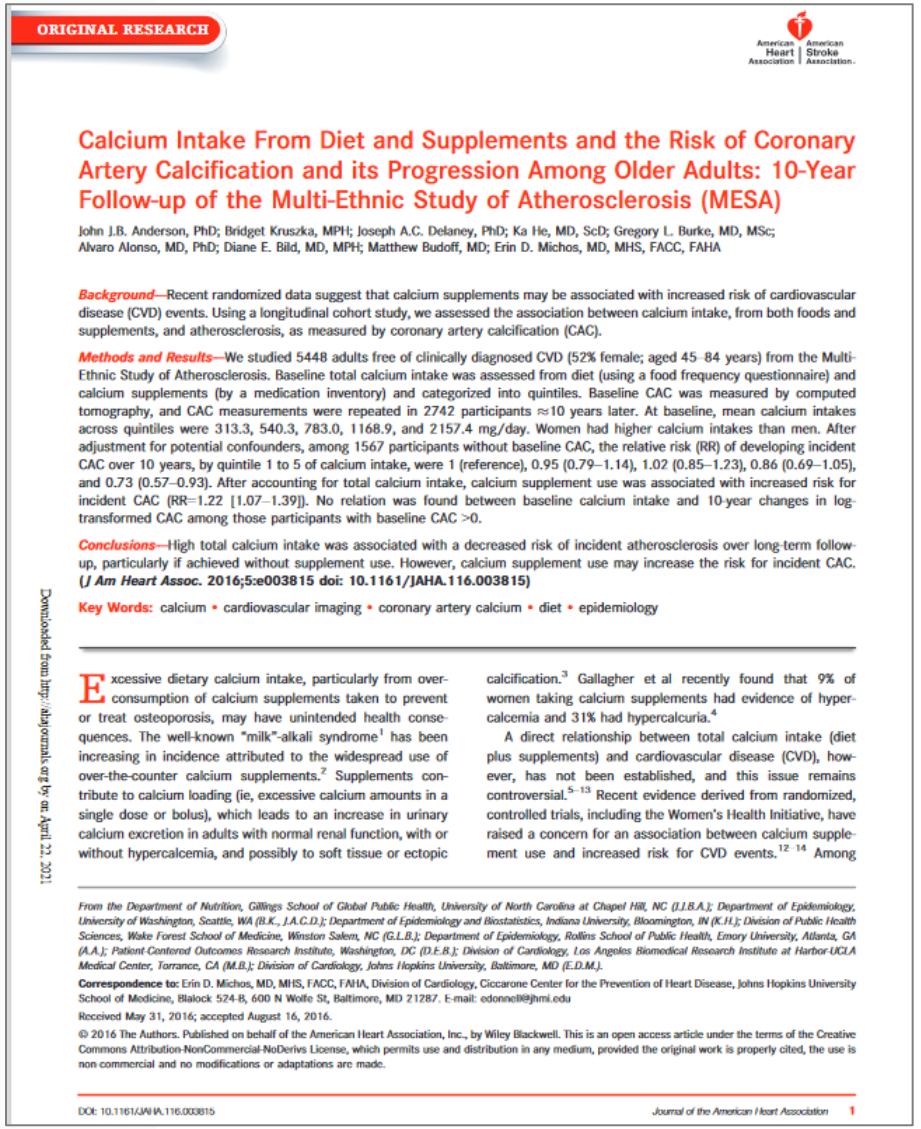
Keywords: vitamin K_2; postmenopausal women; undercarboxylated osteocalcin; femoral neck; bone mineral density (BMD)

OSTEOPOROSI

Gli integratori di Calcio

Lo studio del 2016 sul *J. of the American Heart Association* sostiene che **adeguati livelli di calcio dalla dieta proteggono dall'aterosclerosi, ma in chi fa uso di integratori a base di calcio può andare incontro all'effetto opposto.**

Articolo: JJB Anderson et al. Calcium Intake From Diet and Supplements and the Risk of Coronary Artery Calcification and its Progression Among Older Adults: 10-Year Follow-up of the Multi-Ethnic Study of Atherosclerosis (MESA). Journal of the American Heart Association. 2016 (5) 10,



ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Calcium Intake From Diet and Supplements and the Risk of Coronary Artery Calcification and its Progression Among Older Adults: 10-Year Follow-up of the Multi-Ethnic Study of Atherosclerosis (MESA)

John J.B. Anderson, PhD; Bridget Kruszka, MPH; Joseph A.C. Delaney, PhD; Ka He, MD, ScD; Gregory L. Burke, MD, MSc; Alvaro Alonso, MD, PhD; Diane E. Bild, MD, MPH; Matthew Budoff, MD; Erin D. Michos, MD, MHS, FACC, FAHA

Background—Recent randomized data suggest that calcium supplements may be associated with increased risk of cardiovascular disease (CVD) events. Using a longitudinal cohort study, we assessed the association between calcium intake, from both foods and supplements, and atherosclerosis, as measured by coronary artery calcification (CAC).

Methods and Results—We studied 5448 adults free of clinically diagnosed CVD (52% female; aged 45–84 years) from the Multi-Ethnic Study of Atherosclerosis. Baseline total calcium intake was assessed from diet (using a food frequency questionnaire) and calcium supplements (by a medication inventory) and categorized into quintiles. Baseline CAC was measured by computed tomography, and CAC measurements were repeated in 2742 participants ≈10 years later. At baseline, mean calcium intakes across quintiles were 313.3, 540.3, 783.0, 1168.9, and 2157.4 mg/day. Women had higher calcium intakes than men. After adjustment for potential confounders, among 1567 participants without baseline CAC, the relative risk (RR) of developing incident CAC over 10 years, by quintile 1 to 5 of calcium intake, were 1 (reference), 0.95 (0.79–1.14), 1.02 (0.85–1.23), 0.86 (0.69–1.05), and 0.73 (0.57–0.93). After accounting for total calcium intake, calcium supplement use was associated with increased risk for incident CAC (RR=1.22 [1.07–1.39]). No relation was found between baseline calcium intake and 10-year changes in log-transformed CAC among those participants with baseline CAC >0.

Conclusions—High total calcium intake was associated with a decreased risk of incident atherosclerosis over long-term follow-up, particularly if achieved without supplement use. However, calcium supplement use may increase the risk for incident CAC.
(*J Am Heart Assoc.* 2016;5:e003815 doi: 10.1161/JAHA.116.003815)

Key Words: calcium • cardiovascular imaging • coronary artery calcium • diet • epidemiology

Excessive dietary calcium intake, particularly from over-consumption of calcium supplements taken to prevent or treat osteoporosis, may have unintended health consequences. The well-known "milk"-alkali syndrome[1] has been increasing in incidence attributed to the widespread use of over-the-counter calcium supplements.[2] Supplements contribute to calcium loading (ie, excessive calcium amounts in a single dose or bolus), which leads to an increase in urinary calcium excretion in adults with normal renal function, with or without hypercalcemia, and possibly to soft tissue or ectopic calcification.[3] Gallagher et al recently found that 9% of women taking calcium supplements had evidence of hypercalcemia and 31% had hypercalciuria.[4]

A direct relationship between total calcium intake (diet plus supplements) and cardiovascular disease (CVD), however, has not been established, and this issue remains controversial.[5–13] Recent evidence derived from randomized, controlled trials, including the Women's Health Initiative, have raised a concern for an association between calcium supplement use and increased risk for CVD events.[12–14] Among

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OSTEOPOROSI

Agenzia Italiana del Farmaco

Effetti cardiovascolari del supplemento di calcio nella prevenzione e nel trattamento dell'osteoporosi. Un'analisi pubblicata su Nature Endocrinology

L'uso di integratori di calcio per prevenire l'osteoporosi continua ad essere dibattuto sia per quanto riguarda l'efficacia che per la sicurezza. In un editoriale pubblicato su *Nature Reviews Endocrinology*, Ian R. Reid, della Facoltà di Scienze Mediche e della Salute dell'Università di Auckland (New Zealand), si sofferma in particolare sulla correlazione tra supplementi di calcio e rischio cardiovascolare. Recenti studi clinici, meta-analisi e studi osservazionali hanno evidenziato che l'uso di integratori di calcio può aumentare il rischio di infarto del miocardio e di ictus. Una nuova meta-analisi suggerisce, invece, che non vi sarebbe alcun problema con gli integratori di calcio, ma tale studio – afferma Reid – include dati controversi omessi dalle analisi precedenti, per cui il dibattito è destinato a proseguire.

"Se utilizzati da soli, - scrive l'Autore –gli integratori di calcio sembra aumentino il rischio di frattura dell'anca; se usati in combinazione con la vitamina D, riducono il rischio di tali fratture solo nei soggetti che hanno livelli molto bassi di vitamina D[1].

Per quanto riguarda la loro sicurezza, esistono almeno altre tre preoccupazioni. Lo studio Women's Health Initiative (WHI) ha mostrato che l'uso di integratori di calcio in combinazione con la vitamina D aumenta il rischio di calcoli renali del 17%, causando più calcoli rispetto al numero di fratture prevenute[2]. Effetti avversi gastrointestinali sono stati riconosciuti come una spiacevole complicazione dell'uso di integratori di calcio prolungato negli anni. Uno studio del 2012 ha riportato un rischio due volte maggiore di ricovero in ospedale con una situazione di emergenza gastrointestinale acuta in un gruppo di pazienti randomizzati a ricevere supplementi di calcio; ancora una volta, questi integratori hanno causato più ricoveri ospedalieri rispetto alle fratture prevenute. Questo primo bilancio – scrive Reid – suggerisce che gli integratori di calcio, con o senza vitamina D, non hanno un beneficio netto. Tuttavia, un terzo problema di sicurezza, infarto del miocardio (e forse ictus), ha ultimamente dominato la discussione. Questi eventi avversi sono venuti alla luce per la prima volta nell'*Auckland Calcium Study* e sono stati confermati in due successive meta-analisi di studi che valutavano gli effetti del calcio in monoterapia. La questione se l'uso di integratori di calcio in combinazione con la vitamina D abbia o meno anche un effetto negativo sugli esiti cardiovascolari è più controversa. La risposta potrebbe essere trovata nello studio WHI, a seconda di come i dati vengono analizzati, in quanto questo – prosegue l'Autore – è di gran lunga il più grande studio in questo settore condotto fino ad oggi.

L'osteoporosi e gli integratori di Calcio

PARERE AIFA:

Pareri discordanti sulla relazione tra utilizzo di integratori a base di CALCIO nel trattamento dell'osteoporosi e **l'AUMENTATO RISCHIO** di formazione di placche nelle arterie e di danni al cuore

→ Probabile aumento del rischio di infarto del miocardio e di ictus??

Tratto da: https://www.aifa.gov.it/-/effetti-cardiovascolari-del-supplemento-di-calcio-nella-prevenzione-e-nel-trattamento-dell-osteoporosi-un-analisi-pubblicata-su-nature-endocrinology

OSTEOPOROSI

AIFA Agenzia Italiana del Farmaco

Tuttavia – conclude l'Autore – gran parte di questa discussione è accademica, in quanto non vi è probabilmente nessun beneficio netto nell'uso di integratori di calcio, indipendentemente dai loro effetti cardiovascolari, poichè la loro bassa efficacia è più che controbilanciata dai loro effetti negativi sui calcoli renali e sui disturbi gastrointestinali. Pertanto, la controversia sulla sicurezza cardiovascolare di integratori di calcio non è la questione critica, ma solo un altro motivo per dirigere i pazienti a rischio di fratture osteoporotiche nei confronti di altri interventi più sicuri che hanno dimostrato di ridurre le fratture".

***CONCLUSIONE:** in caso di osteoporosi*

*meglio **NON** usare gli integratori di CALCIO vista la loro bassa efficacia e gli effetti negativi sui **CALCOLI RENALI (ipercalcemia)**, sui DISTRURBI GASTROINTESTINALI e possibili **effetti cardiovascolari.***

2 DEMENZA

I livelli sierici di 25-idrossivitamina D nei pazienti con **malattia di Alzheimer** sono più bassi rispetto a quelli dei pazienti sani anziani [1],

[1]

Journal of Alzheimer's Disease 37 (2013) 147–171
DOI 10.3233/JAD-130452
IOS Press

Meta-Analysis of Memory and Executive Dysfunctions in Relation to Vitamin D

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[d]*Epidemiology and Public Health Group, University of Exeter Medical School, Exeter, United Kingdom*
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Handling Associate Editor: William Grant

Accepted 8 May 2013

Abstract.
Background: Hypovitaminosis D is associated with global cognitive impairment in adults. It remains unclear which domain-specific cognitive functions are affected with hypovitaminosis D.
Objective: To systematically review and quantitatively synthesize the association of serum 25-hydroxyvitamin D (25OHD) concentrations with episodic memory and executive functions in adults.
Methods: A Medline and PsycINFO® libraries search was conducted on May 2012, with no limit of date, using the Medical Subject Headings (MeSH) terms "Vitamin D" OR "Hydroxycholecalciferols" combined with the MeSH terms "Memory" OR "Memory Disorders" OR "Executive Function" OR "Attention" OR "Cognition" OR "Cognition disorders" OR "Dementia" OR "Alzheimer disease" OR "Neuropsychological Tests". Fixed-effects meta-analysis was performed from 12 eligible studies using an inverse-variance method.
Results: Of the 285 selected studies, 14 observational studies (including 3 prospective cohort studies) and 3 interventional studies met the selection criteria. All were of good quality. The number of participants ranged from 44–5,692 community-dwellers (0–100% women). In the pooled analysis, although episodic memory disorders showed only modest association with lower 25OHD concentrations (summary effect size of the difference (ES) = −0.09 [95%CI: −0.16; −0.03]), associations of greater magnitude were found with executive dysfunctions (processing speed: mean difference of Trail Making Test (TMT)-A score = 4.0 [95%CI: 1.20;6.83]; mental shifting: mean difference of TMT-B score = 12.47 [95%CI: 6.78;18.16]; information updating tests: ES = −0.31 [95%CI: −0.5; −0.09]). The pooled risk of incident decline of TMT-B score was OR = 1.25 [95%CI: 1.05;1.48] in case of initial lower 25OHD concentrations. Vitamin D repletion resulted in improved executive functions (ES = −0.50 [95%CI: −0.69; −0.32] for before-and-after comparison), but exhibited no difference with control groups (ES = 0.14 [95%CI: −0.04;0.32] for between-group comparison after intervention).
Conclusion: Lower serum 25OHD concentrations predict executive dysfunctions, especially on mental shifting, information updating and processing speed. The association with episodic memory remains uncertain.

Keywords: Aging, cognition, episodic memory, executive functions, meta-analysis, neuroendocrinology, vitamin D

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[1] Annweiler C, Montero-Odasso M, Llewellyn DJ, Richard-Devantoy S, Duque G, Beauchet O. Meta-analysis of memory and executive dysfunctions in relation to vitamin D. J Alzheimers Dis2013;37:147–71

2 DEMENZA

I livelli **bassi di vitamina D3 sono associati ad una funzione cognitiva peggiore** e ad un aumentato rischio di sviluppare la malattia di Alzheimer [2].

[2]

VIEWS & REVIEWS

Vitamin D, cognition, and dementia

A systematic review and meta-analysis

Cynthia Balion, PhD
Lauren E. Griffith, PhD
Lisa Strifler, BSc
Matthew Henderson, PhD
Christopher Patterson, MD
George Heckman, MD
David J. Llewellyn, PhD
Parminder Raina, PhD

Correspondence & reprint requests to Dr. Balion: balion@phac.ca

ABSTRACT

Objective: To examine the association between cognitive function and dementia with vitamin D concentration in adults.

Methods: Five databases were searched for English-language studies up to August 2010, and included all study designs with a comparative group. Cognitive function or impairment was defined by tests of global or domain-specific cognitive performance and dementia was diagnosed according to recognized criteria. A vitamin D measurement was required. Two authors independently extracted data and assessed study quality using predefined criteria. The Q statistic and I^2 methods were used to test for heterogeneity. We conducted meta-analyses using random effects models for the weighted mean difference (WMD) and Hedge's g.

Results: Thirty-seven studies were included; 8 contained data allowing mean Mini-Mental State Examination (MMSE) scores to be compared between participants with vitamin D <50 nmol/L to those with values ≥50 nmol/L. There was significant heterogeneity among the studies that compared the WMD for MMSE but an overall positive effect for the higher vitamin D group (1.2, 95% confidence interval [CI] 0.5 to 1.9; $I^2 = 0.65$; $p = 0.002$). The small positive effect persisted despite several sensitivity analyses. Six studies presented data comparing Alzheimer disease (AD) to controls but 2 utilized a method withdrawn from commercial use. For the remaining 4 studies the AD group had a lower vitamin D concentration compared to the control group (WMD = −6.2 nmol/L, 95% CI −10.6 to −1.8) with no heterogeneity ($I^2 < 0.01$; $p = 0.53$).

Conclusion: These results suggest that lower vitamin D concentrations are associated with poorer cognitive function and a higher risk of AD. Further studies are required to determine the significance and potential public health benefit of this association. Neurology® 2012;79:1397–1405

GLOSSARY

AD = Alzheimer disease; **CI** = confidence interval; **CPBA** = competitive protein binding assay; **GDNF** = glial cell derived neurotrophic factor; **iNOS** = nitric oxide synthase; **MMSE** = Mini-Mental State Examination; **NGF** = nerve growth factor; **NINCDS-ADRDA** = National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; **PTH** = parathyroid hormone; **RCT** = randomized controlled trial; **RIA** = radioimmunoassay; **WMD** = weighted mean difference.

Vitamin D insufficiency may be a modifiable risk factor for dementia as the role of vitamin D in brain function is becoming clearer.[1,2] At the molecular level, the brain has the ability to synthesize the active form of vitamin D (1,25-dihydroxyvitamin D) within many cell types and regions with predominance in the hypothalamus and the large neurons within the substantia nigra.[3] Many genes are regulated by vitamin D allowing cells to synthesize relevant products in response to routine signals and stimuli, demonstrating that vitamin D acts as an autocrine and paracrine agent.[4] Functionally, vitamin D contributes to neuroprotection by modulating the production of nerve growth factor (NGF),[5] neurotrophin 3,[5] glial cell derived neurotrophic factor (GDNF),[6] nitric oxide synthase (iNOS),[7] and choline acetyl transferase.[8]

From the Departments of Pathology and Molecular Medicine (C.B., M.H.), Clinical Epidemiology and Biostatistics (L.E.G., L.S., P.R.), and Medicine (C.P.), and R. Samuel McLaughlin Center on Gerontological Research and Education (P.R.), McMaster University, Hamilton; Department of Health Studies and Gerontology (G.H.), University of Waterloo, Schlegel-UW Research Institute for Aging, Kitchener, Canada and Peninsula College of Medicine and Dentistry (D.J.L.), University of Exeter, Devon, UK.

Study funding: Ontario Research Coalition of Research Institutes/Centres on Health & Aging, Ontario Ministry of Long Term Care. Parminder Raina holds a Canada Research Chair in GeroScience and Raymond and Margaret Labarge Chair in Research and Knowledge Application for Optimal Aging.

Go to Neurology.org for full disclosures. Disclosures deemed relevant by the authors, if any, are provided at the end of this article.

Supplemental data at www.neurology.org

Supplemental Data

Podcast

[1] Balion C, Griffith LE, Strifler L, et al. Vitamin D, cognition, and dementia: a systematic review and meta-analysis. Neurology 2012;79:1397–405

3 IMMUNOSTIMOLANTE

La supplementazione di Vit D può **ridurre il rischio di contrarre l'influenza** e le **infezioni virali, come COVID-19**

nutrients MDPI

Review

Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths

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Abstract: The world is in the grip of the COVID-19 pandemic. Public health measures that can reduce the risk of infection and death in addition to quarantines are desperately needed. This article reviews the roles of vitamin D in reducing the risk of respiratory tract infections, knowledge about the epidemiology of influenza and COVID-19, and how vitamin D supplementation might be a useful measure to reduce risk. Through several mechanisms, vitamin D can reduce risk of infections. Those mechanisms include inducing cathelicidins and defensins that can lower viral replication rates and reducing concentrations of pro-inflammatory cytokines that produce the inflammation that injures the lining of the lungs, leading to pneumonia, as well as increasing concentrations of anti-inflammatory cytokines. Several observational studies and clinical trials reported that vitamin D supplementation reduced the risk of influenza, whereas others did not. Evidence supporting the role of vitamin D in reducing risk of COVID-19 includes that the outbreak occurred in winter, a time when 25-hydroxyvitamin D (25(OH)D) concentrations are lowest; that the number of cases in the Southern Hemisphere near the end of summer are low; that vitamin D deficiency has been found to contribute to acute respiratory distress syndrome; and that case-fatality rates increase with age and with chronic disease comorbidity, both of which are associated with lower 25(OH)D concentration. To reduce the risk of infection, it is recommended that people at risk of influenza and/or COVID-19 consider taking 10,000 IU/d of vitamin D_3 for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000 IU/d. The goal should be to raise 25(OH)D concentrations above 40–60 ng/mL (100–150 nmol/L). For treatment of people who become infected with COVID-19, higher vitamin D_3 doses might be useful. Randomized controlled trials and large population studies should be conducted to evaluate these recommendations.

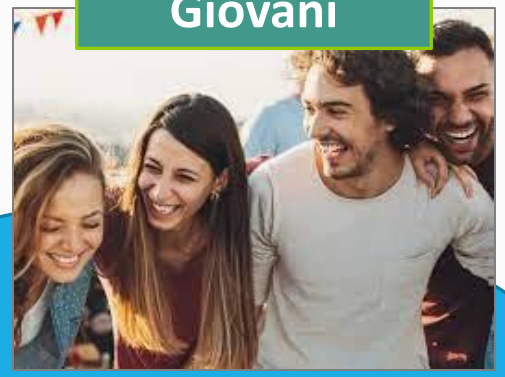
Keywords: acute respiratory distress syndrome (ARDS); ascorbic acid; cathelicidin; coronavirus; COVID-19; cytokine storm; influenza; observational; pneumonia; prevention; respiratory tract infection; solar radiation; treatment; UVB; vitamin C; vitamin D

1. Introduction

The world is now experiencing its third major epidemic of coronavirus (CoV) infections. A new CoV infection epidemic began in Wuhan, Hubei, China, in late 2019, originally called 2019-nCoV [1]

PAZIENTE

Giovani



Donne in menopausa

Armidik

Anziani

APPROFONDIMENTO SCIENTIFICO E MECCANISMO D'AZIONE

VITAMINA D3

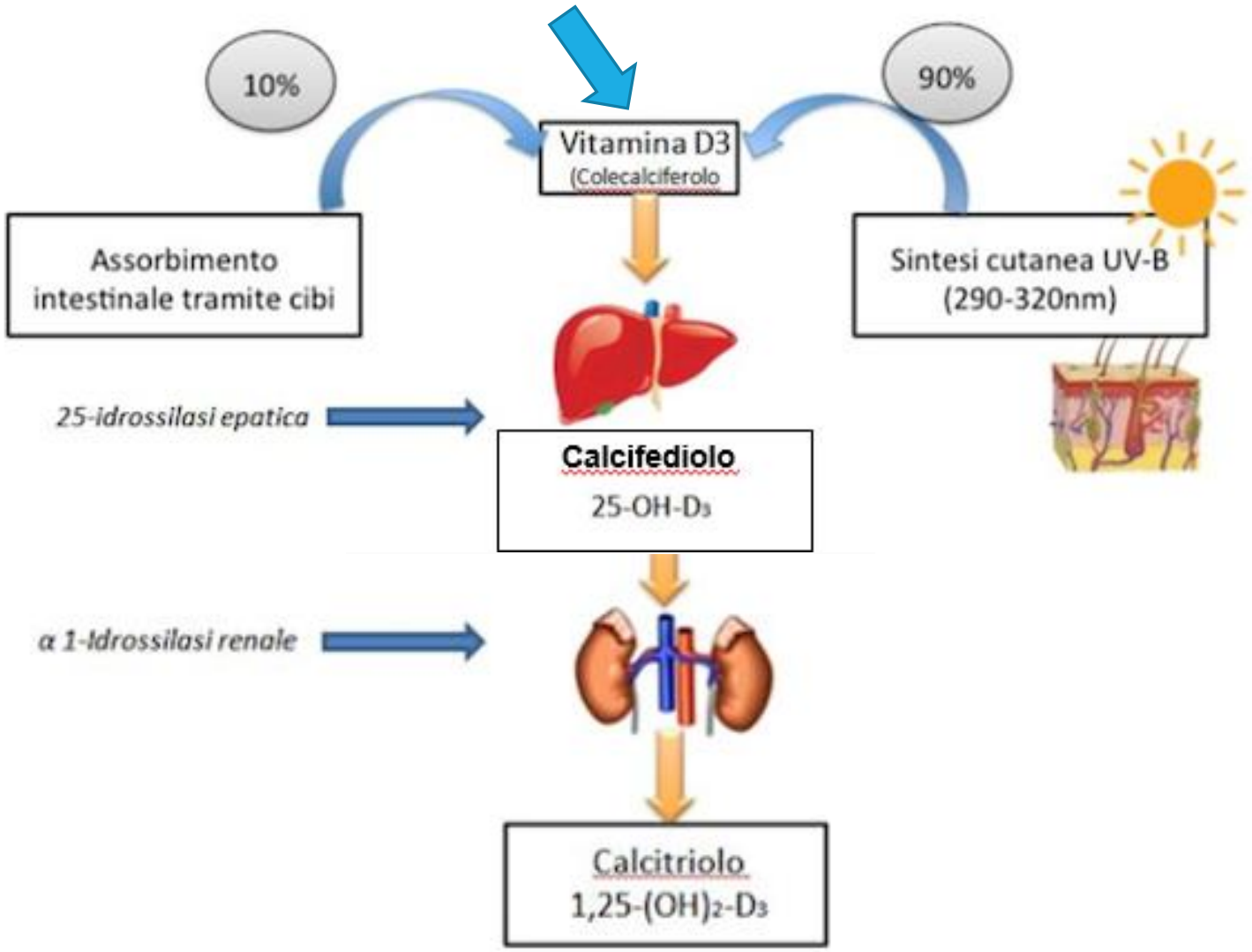
VITAMINA K2

VITAMINA D3

La **vitamina D3**, nota anche come **colecalciferolo,** è una vitamina liposolubile che, oltre ad essere assunta con la dieta, viene **sintetizzata nella pelle** dal 7-deidrossicolesterolo attraverso una **serie di reazioni fotochimiche che usano le radiazioni UVB della luce solare.**

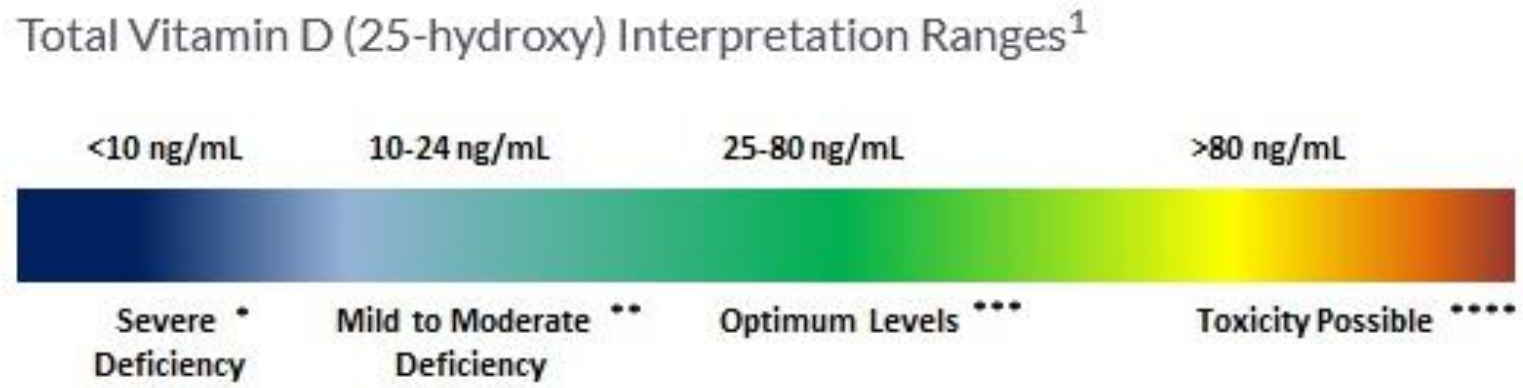
VITAMINA D3

Armidik



VITAMINA D3

Lo stato vitaminico D può essere misurato con un semplice esame del sangue che valuti i livelli di **CALCIFEDIOLO**, il metabolita epatico del colecalciferolo.



Si definisce **ipovitaminosico D** l'individuo con un livello di calcifediolo **inferiore a 30 nanogrammi (ng) per millilitro.**

In situazioni di carenza di vitamina D3, si attiva la rimozione di calcio dallo scheletro.

1. http://cclnprod.cc.nih.gov/dlm/testguide.nsf/Index/353F860EA5F1704585256BA700666862?OpenDocument/

VITAMINA D3

FUNZIONI DELLA VITAMINA D

- ✓ aumenta l'efficienza dell'assorbimento intestinale di calcio e fosforo
- ✓ favorisce una corretta mineralizzazione dell'osso, ma il suo effetto è principalmente indiretto: facilitando l'assorbimento intestinale di calcio e lo mette a disposizione dell'osso
- ✓ promuove la differenziazione cellulare ossea

VITAMINA D3

ALTRE FUNZIONI DELLA VITAMINA D3

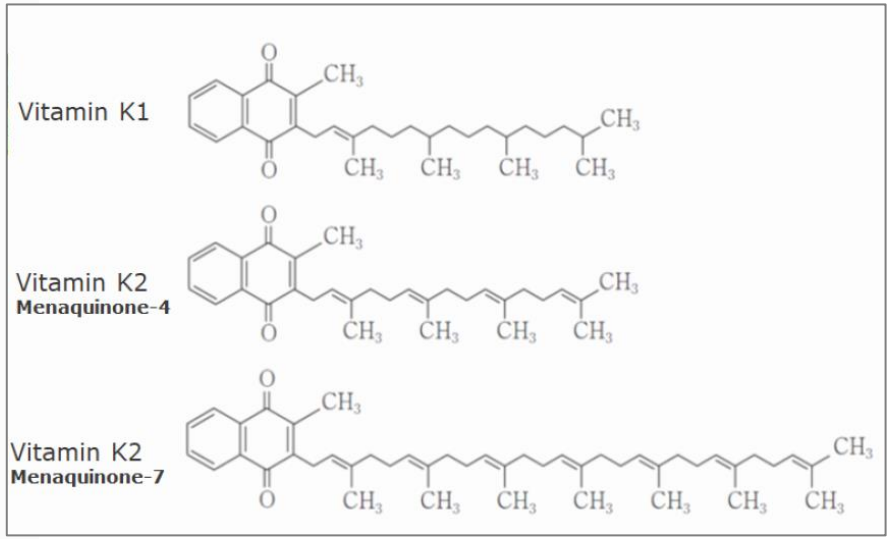
-->> inoltre rilascia i neurotrasmettitori (come la serotonina) che aiutano a **MODULARE POSITIVAMENTE L'UMORE.**

-->> azione **IMMUNOMODULATORIA ED ANTINFIAMMATORIA**
La vitamina D3 attiva quei geni che regolano il **SISTEMA IMMUNITARIO.**
Da recenti studi, la vitamina D è in grado di ridurre il rischio di infezioni respiratorie di origine virale in quanto sembra capace di contrastare il danno polmonare da iper-infiammazione

VITAMINA K2

La vitamina K ha diverse forme:

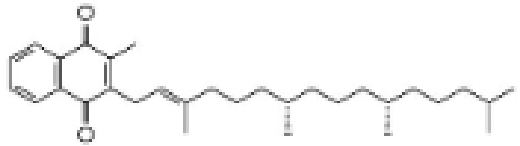
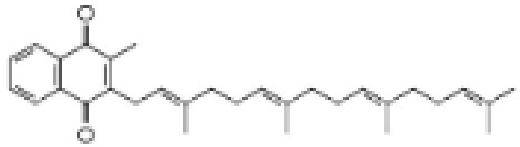
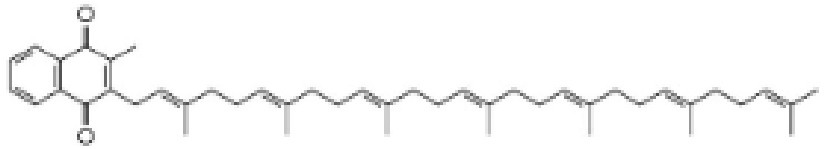
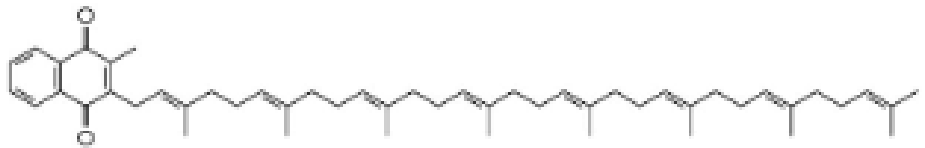
- vitamina K1 (fillochinone),
- vitamina K2 (menachinone)
- e vitamina K3 (Menadione idrosolubile).



LA VITAMINA K2 (menachinone) è di origine batterica, creata dai batteri che popolano il colon umano e assorbita in loco.

- ✓ **E' essenziale per il benessere delle ossa**
- ✓ **La forma biologicamente attiva è la MK-7**
- ✓ **La vitamina K2 MK-7 è presente in alimenti ricchi di grasso come uova, formaggi, latte e carne rossa ma la catena alimentare deve provenire da animali da pascolo in libertà, poi anche in molta quantità nel formaggio fermentato e nel natto (soia fermentata) presente in Giappone.**

VITAMINA K2

Vitamin K isoform	Structure	$K_{1/2}$ in cells	$T_{1/2}$ in blood	Primary source in food
Vitamin K1 Phylloquinone (K-1)		12.3µM	~ 3 hours	Leafy greens e.g. spinach, kale
Vitamin K2 Menaquinone-4 (MK-4)		3.6µM	~ 1.5 hours	Meat and dairy e.g. beef, poultry, butter, soft cheese
Vitamin K2 Menaquinone-7 (MK-7)		1.9µM	~ 70 hours	Fermented foods and dairy e.g. natto, hard cheese, sauerkraut
Vitamin K2 Menaquinone-8 (MK-8)		1.4µM	~ 70 hours	Fermented foods and dairy e.g. natto, hard cheese, sauerkraut

Tratto da: Akbulut et al.Vitamin K2 Needs an RDI Separate from Vitamin K1.Nutrient. 2020.

VITAMINA K2

IL MIGLIORE È IL MENACHINONE -7 (MK-7).

nutrients

MDPI

Review

MK-7 and Its Effects on Bone Quality and Strength

Toshiro Sato [1,*], Naoko Inaba [1] and Takatoshi Yamashita [2]

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check for updates

5. Advantages of MK-7

Osteocalcin has been used as a biomarker for bone metabolism. Vitamin K deficiency leads to an increase in serum ucOC, and a high serum ucOC level has been associated with hip fractures [50,51], and has been recognized as an independent risk factor for fractures. Since 2007, serum ucOC has been used as a diagnostic marker to evaluate vitamin K deficiency in bones in Japan. A smaller dose of MK-7 can γ-carboxylate OC compared to doses of K1 or MK-4. A supplemental intake of 250–1000 μg/day of vitamin K1 activates OC [52], which is higher than the current RDIs of vitamin K in most countries. A markedly higher dose of MK-4 (600–1500 μg/day) is required to activate OC [53,54], as it has been shown to have a very short half-life in humans [37] and it is poorly absorbed [55]. Nutritional doses of MK-4, such as the consecutive intake of 60 μg/day or a single intake of 420 μg, have shown to be ineffective [55]. In contrast, MK-7 at doses around the current RDI (90–180 μg/day) promoted OC carboxylation [35,38,56]. A study demonstrated that MK-7 derived from natto has a very long half-life in the serum and induces more complete carboxylation of OC compared to vitamin K1 in humans [57].

6. Conclusions

Among vitamin K homologs, MK-7 has been shown to have the highest bioavailability and the most significant effect on OC carboxylation in humans. Vitamin K1 and MK-4 at their current RDIs are not sufficient for activation of OC. On the other hand, it is expected that MK-7 may promote bone health.

VITAMINA K2

La vitamina K principalmente funziona come

COAGULAZIONE DEL SANGUE

La vitamina K principalmente funziona come un **coenzima per la sintesi delle proteine coinvolte nella coagulazione del sangue e metabolismo osseo**.

La **protrombina**, nota anche come fattore II, interviene nel processo di riparazione dei danni ai vasi sanguigni ed **è una proteina vitamina K-dipendente di vitale importanza per la coagulazione del sangue**. *I pazienti che assumono anticoagulanti, come il warfarin (Coumadin in Italia), devono evitare la supplementazione di vitamina K.*

VITAMINA K2

La vitamina K principalmente funziona come

MIGLIORA la mineralizzazione ossea

MK-7 interviene come cofattore nelle reazioni di gamma carbossilazione che attivano **l'Osteocalcina,** una proteina sintetizzata dagli Osteoblasti, che lega il Calcio e risulta indispensabile per la mineralizzazione e la crescita dell'osso.

INIBISCE la calcificazione arteriosa

Negli ultimi anni i ricercatori hanno scoperto sempre più informazioni sulla **MGP, cioè la matrice GLA proteica**, una proteina sempre dipendente dalla vitamina K e presente nelle pareti dei vasi sanguigni, ossa e cartilagine.

La vitamina K attiva il MGP (la matrice GLA proteica) che aiuta il calcio a dirigersi ai luoghi desiderabili (osso) e tenerlo invece lontano dell'accumulo nelle arterie

ARMIDAL SRL

Armidik

POSOLOGIA IN GOCCE

Versatilità delle modalità d'uso

Prevenzione:

- 1 gtt al giorno = 1000 U.I.
- 10 gtt alla settimana = 10000 U.I.
- 50 gtt una volta al mese = 50000 U.I.

ARMIDAL SRL

Armidik

POSOLOGIA

Modalità d'uso

si consiglia l'assunzione di 1 o 2 gocce al giorno a stomaco pieno.

- ✓ **Senza glutine**
- ✓ **Naturalmente privo di lattosio**
- ✓ **Adatto ai diabetici (senza zucchero)**

Confezione da 10ml

CONTROINDICAZIONI E INTERAZIONI FARMACOLOGICHE

CONTROINDICAZIONI

- ***Ipersensibilità alla vitamina D3 e vitamina K2.***
- ***Calcolosi renale***
- ***Insufficienza renale grave***: questi soggetti hanno un alterato metabolismo della vitamina D, perciò, se devono essere trattati con colecalciferolo, è necessario monitorare gli effetti sull'omeostasi di calcio e fosforo.

INTERAZIONI FARMACOLOGICHE

1. ***Digitale e glicosidi cardiaci:*** la somministrazione di VITADIK può aumentare il rischio di tossicità della digitale (aritmia). E' quindi consigliato il monitoraggio elettrocardiografico e delle concentrazioni sieriche di calcio.
2. ***Walfarin (o Coumadin) :*** vietata l'assunzione contemporanea del VITADIK
3. ***Diuretici tiazidici***: sono farmaci che riducono l'eliminazione urinaria del calcio, quindi è raccomandato il controllo delle concentrazioni sieriche del calcio.