

Rhematoid Arthrits Effects Associated with Hypovitaminosis K

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Abstract

Background: *Rheumatoid arthritis (RA) is a progressive inflammatory autoimmune disease with articular and systemic effects. Its exact cause is unknown, but genetic and environmental factors are contributory. Although some patients have mild self-limited disease, many experience joint destruction, severe physical disability and multiple co-morbidities. T cells, B cells and the interaction of pro-inflammatory cytokines play key roles in the pathophysiology of RA. In addition to the effect of vitamin K on blood coagulation, several studies have indicated the important role of vitamin K in bone metabolism and bone protection. Vitamin K functions as a coenzyme for vitamin K-dependent carboxylase, an enzyme required for the synthesis of proteins involved in hemostasis (blood clotting) and bone metabolism. Matrix Gla-protein, a vitamin K-dependent protein present in vascular smooth muscle, bone, and cartilage, is the focus of considerable scientific research because it might help reduce abnormal calcification. Osteocalcin is another vitamin K-dependent protein that is present in bone and may be involved in bone mineralization or turnover. There is evidence of a correlation between low serum levels of vitamin k and a high incidence of femoral neck and vertebral fractures*

Keywords: *Rheumatoid Arthritis (RA), Vitamin K, Osteoporotic Changes.*

Rheumatoid Arthritis

Definition:

Rheumatoid Arthritis is a systemic autoimmune disease of unknown etiology. It is characterized by chronic inflammatory process that affects primarily synovial membrane of joints. It is a symmetric polyarthritis affecting mainly small joints of the hands, wrists, elbows and knees. It is a progressive disease that if untreated properly may cause irreversible joints deformity and subsequently loss of function and disability. (1).

RA may also affect other body systems such as cardiovascular system, pulmonary, ocular, nervous, reticulo-endothelial, urinary and other systems. These symptoms are known as extra-articular manifestations. (2).

Epidemiology:

RA is the most common type of chronic inflammatory arthritis. It has a prevalence rate ranging from 0.3 to 1 % of population. (2).

The average annual incidence of RA in the United States is 3 per 10000 persons per year. (3).

Racial factor plays an important role in RA prevalence. Researchers tried to calculate RA prevalence in Africa by a meta-analytic study and it was 0.3% (3).

RA generally affects women three to five times more than men (4). But this ratio decrease with age (5).

RA is also more common in 35-50 years old patients and its incidence increases with age (6).

Other factors that increase risk of RA is smoking especially in people who are heavy smokers with RF positive. Also, first degree relativity to patients with RA increase risk by 2-3 folds.

Monozygotic twins are 15-20% riskier(7).

Pathogenesis:

Pathogenesis isn't completely clear up till now. An auto-immune reaction occurs in genetically susceptible persons with the help of external triggering factors. (8).

Multiple factors combine together initiating a cascade of events resulting in severe uncontrollable inflammation with subsequent cartilage damage and finally bone erosion. (4)

The starting point of this process is T-cell activation which somehow becomes self-reactive and recognizes self-tissues as synovial sheath of joints. Activated T cells secrete IL2 activating cellular and humoral immune response. Then inflammatory cascade is initiated. (9).

Auto reactive B cells act as antigen presenting cell and their activation whether T-cell dependent or independent leads to autoantibody production and immune complex formation increasing release of pro-inflammatory mediators (10).

Disease specific autoantibodies such as RF (which is an anti IgM class with specificity for the Fc fragment of IgG) or anti cyclic citrulinated protein (anti-CCP) can be found in susceptible persons many years before clinical symptoms start, indicating early self-reactivity of B-cell. (11).

Synovial membrane is the site where immune complexes deposit. These complexes fix complement with positive feedback activating more B-cells. Many cytokines are secreted either by activated T-cells or Natural Killer cells activated by RF. Also, macrophages are involved in cytokines secretion (12).

Inflammatory mediators include interleukin 1 β (IL-1 β), IL-6 and tumor necrosis factor (TNF- α) which are the main cytokines activating several cells as lymphocytes, neutrophils, endothelial cells, osteoclasts, chondrocytes, synoviocytes(13).

Also, TNF α which stimulates activation of fibroblast-like synoviocytes. (14).

Both IL-1 and TNF α increase adhesion molecules on endothelial cells, with migration of leukocytes and inflammatory infiltrate into the inflamed joint. They also cause new angiogenesis that characterize rheumatoid synovitis. They induce synthesis and release of enzymes from synovial fibroblasts and articular chondrocytes causing tissue destruction. So, IL-1 is destructive, while TNF- α is inflammatory (15.).

IL-32 activates nuclear factor (NF κ B) producing many pro-inflammatory cytokines and chemokines, such as TNF- α , IL-1, IL-6, and IL-8. (16).

With more inflammation, the synovium becomes completely destroyed. It becomes edematous with more villi and referred to as pannus. Cellular pannus is locally invasive and erosive thanks to proteolytic enzymes produced by synoviocytes in the pannus. (17).

The net result is destruction of articular surfaces cartilage and bone. With progression of inflammation, the destruction may exceed joints and involve other tissues (7)

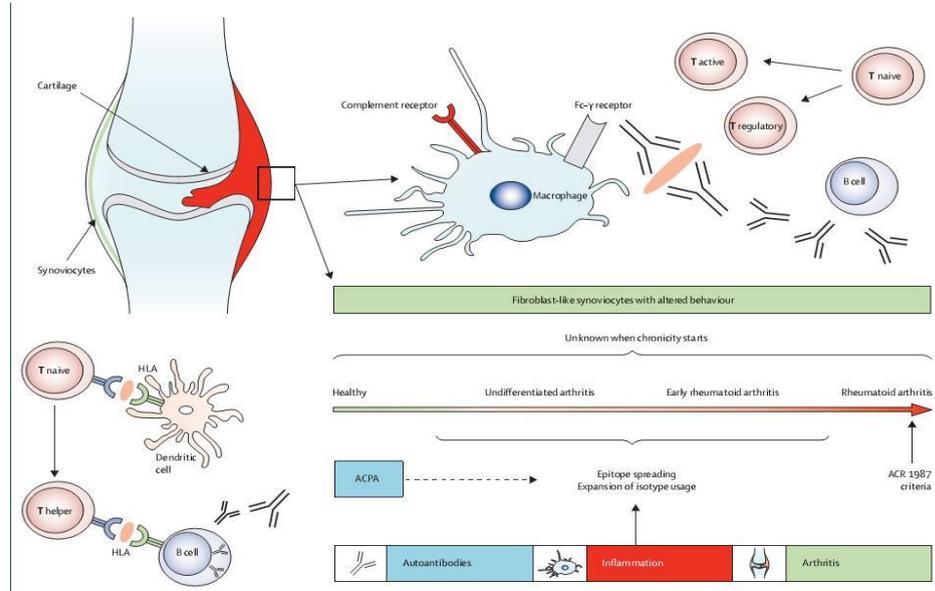


Figure (1): pathological changes in the synovium in rheumatoid arthritis (15).

ACPA: Anti-citrullinated protein ab.

ACR: American college of rheumatology.

Osteoporosis

Definition:

Osteoporosis is among the world's significant concerns to public health. Osteoporosis is a disease in which the net loss of bone surpasses bone formation, and it occurs in women after estrogen loss in postmenopausal age (17).

In broad terms, osteoporosis is a state of increased fracture risk after minimal trauma resulting from low bone density. It is a silent disease, affecting about 200 million people worldwide and responsible for 8.9 million fractures annually all over the world (18).

Osteoporotic fractures are the most devastating consequence of this disease, which are associated with significant burden of health care cost, morbidity, and mortality. Osteoporotic fractures predominantly occur at major skeletal site such as vertebrae (spine), proximal femur (hip), distal forearm (wrist), or shoulder (19)

Fractures Associated with Osteoporosis:

Osteoporotic fractures include fractures of the vertebrae (spine), proximal femur (hip), and distal forearm (wrist). Burge and colleagues reported that of the more than 2 million fractures projected in 2005, vertebral fractures constituted 27%; wrist fractures 19%; hip fractures 14%; pelvic fractures 7%; and others 33% of the more than 2 million fracture incidents estimated (20).

Hip fractures:

Hip fracture is the most serious osteoporotic fracture because it incurs high medical costs, patient functional impairment, morbidity, and mortality. Hip fractures are strongly associated with low bone mineral density, are more costly to repair, and are responsible for most of disabilities associated with osteoporosis. Hip fractures are often treated at the hospital, which enhances counting and companions.(21)

Vertebrae fractures:

Vertebral fractures might occur during daily chores without any trauma or fall, and they are the predictors of future fracture risk: the probability is fivefold for subsequent vertebral fractures and twofold to threefold for fractures at other sites

The first complaint of the patient might be the loss of height caused by vertebral compression due to fractures, which is more evident in the presence of multiple fractures; this abnormality can be objectively detected by increased occiput-to-wall distance caused by dorsal kyphosis (dowager's hump). The determination of historical height loss (difference between the current height and peak height at an age of 20 years) of 1.5 inches (4 cm) or more and prospective height loss (difference between the current height and a previously documented height measurement) of 0.8 inches (2 cm) or more is important. Multiple vertebral thoracic fractures may result in restrictive lung disease and secondary heart problems. Lumbar fractures may decrease the volumes between the ribs to the pelvis, alter abdominal anatomy, crowd internal organs (particularly the gastrointestinal system, causing gastrointestinal complaints such as premature satiety, reduced appetite, abdominal pain, constipation, and distention); further, back pain (acute and chronic), prolonged disability, poor self-image, social isolation, depression, and positional restriction are other problems created by compression fractures in addition to increased mortality (21).

Epidemiology:

The incidence of osteoporotic fracture varies substantially from one geographical to the other. In United States, 10 million people more than the age of 50 suffer with osteoporosis resulting in about 1.5 million fractures each year. Among all the fragility fractures, hip and vertebral fractures in older adults are associated with an increased risk of mortality (22).

Hip fractures account for 4.5 million osteoporotic fractures in the world annually, which is likely to increase upto 21 million in next 40 years. Vertebral fractures account for 1.4 million cases worldwide(22).

In Europe, 27.6 million people have osteoporosis with more than 3.5 million fractures each year (23)

Globally, the trend in the epidemiology of osteoporotic fractures varies substantially, being highest in North America and Europe, followed by Asia, Middle East, Oceania, Latin America, and Africa (24).

However, provided the fact that a large proportion of the population lives in Asia, it is estimated that more than 50% of osteoporotic fractures globally will occur in Asia by 2050 (24).

Vitamin k Physiology**Introduction:**

Vitamins are chemically unrelated families of organic compounds that are essential in small amounts for normal metabolism. Because vitamins (with the exception of vitamin D) cannot be

synthesized by humans, they need to be ingested in the diet to prevent disorders of metabolism. They are divided into water-soluble and fat-soluble(24).

Vitamin K Requirements:

Most U.S. diets contain an adequate amount of vitamin K (25). Data from the 2011–2012 National Health and Nutrition Examination Survey (NHANES) show that among children and teens aged 2–19 years, the average daily vitamin K intake from foods is 66 mcg. In adults aged 20 and older, the average daily vitamin K intake from foods is 122 mcg for women and 138 mcg for men. When both foods and supplements are considered, the average daily vitamin K intake increases to 164 mcg for women and 182 mcg for men (26).

Some analyses of NHANES datasets from 2003–2006 and 2007–2010 raised concerns about average vitamin K intakes because only about one-third of the U.S. population had a vitamin K intake above the AI (27).

Finally, food composition databases provide information primarily on phylloquinone; menaquinones—either dietary or from bacterial production in the gut—likely also contribute to vitamin K status (25).

Deficiency:

Vitamin K deficiency is rare in the United States. Typically, those afflicted with a deficiency are unable to properly absorb the vitamin K made naturally in the intestinal tract. “People who have severe gastrointestinal disorders, such as gallbladder disease, cystic fibrosis, celiac or Crohn’s disease are unable to properly absorb vitamin K, so they are more susceptible to being deficient. Vitamin K supplements are useful for these medical conditions. Those who take antibiotics for an extended period of time can also experience a lack of vitamin K, according to the NLM.

Antibiotics kill the bacteria that create vitamin K. Babies are not born with the bacteria that create vitamin K, and breast milk is not a good source of the vitamin, according to the University of Maryland Medical Center. Newborn babies in many developed countries are given shots of vitamin K to prevent internal and external bleeding. Deficiency can cause excessive bleeding, which may start from the nose or gums, according to the University of Maryland Medical Center. Other symptoms can include easy bruising, blood in urine and stools. Those experiencing a lack of vitamin K may be instructed by their health care professional to take a supplement. (28).

Uptake of phylloquinone by bone:

Much less is known about the general molecular mechanisms of how lipoproteins deliver lipids and fat-soluble vitamins to extrahepatic tissues such as bone, although there are now studies that have specifically addressed the question of how phylloquinone is delivered to osteoblasts.

The importance of this area for vitamin K centers on knowledge that bone matrix contains several Gla proteins [e.g., osteocalcin, matrix Gla protein (MGP).

Gla-rich protein, and gas 6] that require vitamin K for their function (28) and by findings that undercarboxylated species of osteocalcin and MGP normally circulate in healthy people (29)

Cell culture showed that both primary osteoblasts and osteoblast-like cells could internalize

phylloquinone from all the major lipoprotein fractions in which the order of efficiency of uptake was LDL > TRL > HDL. For reasons already outlined, TRL are likely to be physiologically the most important carrier particle for phylloquinone. The mechanism of cellular uptake of TRL-associated phylloquinone was shown to be dependent on both HSPG and apoE, implying the presence of receptors of the LDLR family on the surface of osteoblasts. The results suggested that mature osteoblasts can effectively take up vitamin K directly from lipoproteins delivered to them in the blood. In support of this concept are findings that the fraction of circulating undercarboxylated species of osteocalcin(ucOC) rapidly decreases in response to dietary phylloquinone supplementation in healthy volunteers.(30).

Osteoporosis and BONE HEALTH:

Osteoporosis, a disorder characterized by porous and fragile bones, is a serious public health problem that affects more than 10 million U.S. adults, 80% of whom are women. Consuming adequate amounts of calcium and vitamin D, especially throughout childhood, adolescence, and early adulthood, is important to maximize bone mass and reduce the risk of osteoporosis. The effect of vitamin K intakes and status on bone health and osteoporosis has been a focus of scientific research. Vitamin K is a cofactor for the gamma-carboxylation of many proteins, including osteocalcin, one of the main proteins in bone (31).

Some research indicates that high serum levels of under carboxylated osteocalcin are associated with lower bone mineral density. Some, but not all, studies also link higher vitamin K intakes with higher bone mineral density and/or lower hip fracture incidence (32).

Although vitamin K is involved in the carboxylation of osteocalcin, it is unclear whether supplementation with any form of vitamin K reduces the risk of osteoporosis. In 2006, Cockayne and colleagues conducted a systematic review and meta-analysis of randomized controlled trials that examined the effects of vitamin K supplementation on bone mineral density and bone fracture(33).

Most of the trials were conducted in Japan and involved postmenopausal women; trial duration ranged from 6 to 36 months. Thirteen trials were included in the systematic review, and 12 showed that supplementation with either phytonadione or MK-4 improved bone mineral density. Seven of the 13 trials also had fracture data that were combined in a meta-analysis. All of these trials used MK-4 at either 15 mg/day (1 trial) or 45 mg/day (6 trials). MK-4 supplementation significantly reduced rates of hip fractures, vertebral fractures, and all nonvertebral fractures. (33).

A subsequent clinical trial found that MK-7 supplementation (180 mcg/day for 3 years) improved bone strength and decreased the loss in vertebral height in the lower thoracic region of the vertebrae in postmenopausal women (34).]

Other randomized clinical trials since the 2006 review by Cockayne have found that vitamin K supplementation has no effect on bone mineral density in elderly men or women. In one of these studies, 381 postmenopausal women received either 1 mg phylloquinone, 45 mg MK-4, or placebo daily for 12 months. All participants also received daily supplements containing 630 mg calcium

and 400 IU vitamin D3. At the end of the study, participants receiving either phylloquinone or MK-4 had significantly lower levels of under carboxylated osteocalcin compared to those receiving placebo. However, there were no significant differences in bone mineral density of the lumbar spine or proximal femur among any of the treatment groups. The authors noted the importance of considering the effect of vitamin D on bone health when comparing the results of vitamin K supplementation studies, especially if both vitamin K and vitamin D (and/or calcium) are administered to the treatment group but not the placebo group (35).

The administration of vitamin D and/or calcium along with vitamin K could partly explain why some studies have found that vitamin K supplementation improves bone health while others have not. In Japan and other parts of Asia, a pharmacological dose of MK-4 (45 mg) is used as a treatment for osteoporosis. The European Food Safety Authority has approved a health claim for vitamin K, noting that “a cause-and-effect relationship has been established between the dietary intake of vitamin K and the maintenance of normal bone (25) The FDA has not authorized a health claim for vitamin K in the United States

Vitamin K and Rheumatoid arthritis:

Rheumatoid arthritis (RA) is a chronic, symmetric polyarticular joint disease that primarily affects the small joints of the hands and feet. It is characterized by infiltration of inflammatory cells such as monocytes and T lymphocytes into the joints, leading to synovial proliferation and progressive destruction of cartilage and bone. It is widely accepted that the progressive destruction of articular cartilage is reliant on the evolution of hyperplastic synovial tissue, and that hyperplasia of fibroblast-like synoviocytes (FLSs) is dependent on dysregulated proliferation and apoptosis (36).

While the role that vitamin K plays in blood clotting is well known, it also functions in important roles for bone and joint health. Clinical studies have documented the long-term effect of 180 mcg of MK-7 in improving bone density and overall bone health(37).

Based upon pre-clinical studies showing another form of vitamin K2 (MK-4) blocked the development of arthritis in the experimental animal model of RA, it was suggested that MK-4 might offer benefit in human RA. Human studies following and it was shown MK-4 supplementation reduced RA disease activity associated with a marked decrease in clinical and biochemical markers. However, since MK-7 has greater bioavailability than MK-4 after oral administration, researchers were quite curious if even better results might be produced with this form (37).

There is evidence that vitamin K2 supplementation reduces inflammation in rheumatoid arthritis by reducing CRP levels. Vitamin K2 may induce apoptosis in rheumatoid arthritis synovial cells. Furthermore, it was reported that MK-4 inhibited the proliferation of fibroblast-like synoviocytes and the development of collagen-induced arthritis in rat models (36).Ebina et al. reported that MK-4 improved disease activity scores in RA patients (38), and it was recently found that MK-7, at a very low concentration, was able to decrease disease activity (37).

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