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Short Communication

Preventing Inflammaging with the Multitasking Vitamin K

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Vitamin K denotes two fat-soluble vitamins, phylloquinone or vitamin K1, and menaquinone or vitamin K2 [1]. Plants and algae produce vitamin K1, and vitamin K2 is predominantly of microbial origin and comprises a family of molecules distinguished from K1 by unsaturated side chains of isoprenoid units varying in length from 1 to 14 repeats (hence, menaquinone-4, menaquinone-7, or MK-4, MK-7). The primary dietary form of vitamin K has been considered K1, whose most abundant source derives from green and leafy vegetables. In contrast, K2 occurs in animal products, meat, dairy, eggs, and fermented food, e.g., cheese, yogurt, and traditional Japanese food natto; it resides in the small and large intestine, where the intestinal microflora, mainly in the small intestine, synthesizes menaquinone-n.

Vitamin K is a multitasking vitamin that facilitates cardiovascular, CNS, immune, metabolic, neuromuscular, and bone-building functions via approximately 18 K-dependent proteins or VKDP [1]. Vitamin K's vital role is in the carboxylation reaction of a VKD protein precursor. This process converts the γ-glutamyl carboxylase of the Glutamic acid or Glu residues of VKD proteins into γ-carboxyglutamate or GLA for specific biological functions. Among other functions: a precursor of the blood clotting prothrombin into thrombin, the prohormone osteocalcin into a calcium building bone matrix, the matrix Gla precursor protein or MGP preventing arterial calcification, the precursor growth arrest-specific six or Gas6 protein into myelin formation in CNS and peripheral nerves.

Besides the family of multitasking proteins, the individual VDK proteins may offer a broad range of biological activities. In addition to its role in a bone matrix formation, osteocalcin increases insulin synthesis, insulin sensitivity, exercise adaptation, testosterone secretion, and male fertility. It also increases the synthesis of neurotransmitters such as dopamine, serotonin, and norepinephrine, improving cognitive and brain development [2].

Vitamin K's broad multitasking and multifunctional roles decline and deteriorate with aging due to several contributing factors. The dysbiosis in gut bacterial flora diminishes the endogenous vitamin K2 production and bioavailability; processed food, antibiotics, food preservatives, and refrigeration deplete beneficial bacteria and the K2 source. The current science on the RDA values for vitamin K, especially K2, is lacking, which compounds the nutritional insufficiency of vitamin K status with aging [3].

The prolonged status of low vitamin K may gradually aggravate the aging process in decline multifunctionality, wear and tear, and chronic inflammation, defined by us as inflammaging. The inflammaging, if not alleviated in the early stages, may lead to a full-blown pathology like osteoporosis, cardiovascular disease, and metabolic and neurodegenerative conditions.

The onset of inflammation may occur in clinically healthy individuals and is often undetected with the inflammatory markers' laboratory data. In one double-blind, randomized three-year clinical trial, 244 healthy 55 to 65 postmenopausal Dutch women received vitamin MK-7, 180 mcg per day [4]. The MK-7 improved the lumbar spine and femoral neck against osteoporotic fracture. The supplement also prevented age-related stiffening of the arteries and improved compliance of the carotid. However, MK-7 did not change the markers of inflammation IL-6, high-sensitive C-reactive protein (hsCRP), tumor necrosis factor-alpha or TNF-alpha, endothelial dysfunction markers, and Advanced Glycation End-products (AGEs).

On the other hand, our in vitro study with vitamin MK-7 dose-dependently inhibited gene expression of TNF-alpha, IL-1alpha, and IL-1beta, inhibiting the TNF-alpha, IL-1alpha, and IL-1beta proteins in healthy human macrophage-derived monocytes or hMDMs [5].

In a double-blind, randomized 12-week trial, we evaluated 20 middle-aged, mixed-gender ambulatory patients from India with peripheral neuropathy due to diabetes Type 2 and vitamin B12 deficiency [6]. The patients received 200 mcg of MK-7 for eight weeks with a total of 12 weeks of evaluation for symptoms of peripheral neuropathy. For the first time, this study provided evidence linking the statistically significant increase in serum levels of vitamin MK-7 to improvement in the debilitating pain and cramps of symptoms of inflammatory peripheral neuropathy in diabetes Type 2 and vitamin B12 deficiency.

These clinical and in vitro studies pointed to the vital role of vitamin K in the prevention of inflammaging and inflammatory conditions. Chronologically bone osteoporosis is the most recognized example of the VKDP biological functions and anti-inflammatory mechanisms.

The inflammation reaction is essential for bone health and disease prevention, regulating the body's universal "master switch" inflammatory mechanism via the nuclear factor- κB or NF-κB [7]. In health, the NF- κB plays a dual role with VKDP osteocalcin building the new bone matrix and, at the same time, disposing of the old bone matrix, allowing remodeling the healthy bone. When the receptor activator of NF-κB or RANK attaches to the "master switch" ligand or LRANK, it turns "ON" the inflammation pathway by the specialized bone cells, the osteoclasts. The opposite occurs when osteoprotegerin blocks RANK, a cytokine upregulated by osteocalcin. Then the "master switch' on osteoclasts is turned "OFF" with the specialized cells osteoblasts building the new bone matrix. The osteocalcin controls the "ON" and "OFF" mechanisms with osteoclasts for bone resorption and osteoblasts for new bone formation and bone remodeling [8].

The role of vitamin K in inhibiting RANK receptors is particularly pronounced with the MK-7 since this form has plasma's half-life significantly longer than other menaquinones and vitamin K1 [9]. In a pre-clinical study, the levels of osteoprotegerin increased with vitamin K1 by 62%, K2 in the form of menaquinone-4 by 247%, and K2 in the form of menaquinone-7 by 329%, indicating that the various forms of vitamin K may have different anti-inflammatory potential moderating NF-κB pathway [9]. The role in blocking RANK and inhibiting TNF alpha, IL-1alpha, IL-1beta, and other markers of inflammation explains, in principle, the systemic mechanism that may prevent the inflammaging with the family of VKDP.

The inflammaging is a new and evolving clinical entity deserving attention in the growing senior population. The distinction between inflammaging and inflammation is in the degree of pathology and may require different diagnostic techniques and therapeutic approaches customized to the needs of the elderly. Vitamin K, especially MK-7, may exemplify a safe and effective supplement with a broad range of clinical efficacy and systematic safety data [10]. Inflammaging and vitamin K address inflammation as a lingering rather than an acute process increasingly attracting clinical attention - the root cause of many diseases that remain poorly understood or treated.

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