The Role of Vitamin K2 in Bone Development for Growing Children

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Abstract

Bone growth is a highly dynamic and complex process beginning before birth and continuing until the early twenties, when the growth plates of bones calcify and close. This period establishes peak bone mass, which significantly influences skeletal health throughout life. Bone development involves three main processes: the formation of bone by osteoblasts, the breakdown of bone by osteoclasts, and the mineralization of bone matrix with calcium. These processes are regulated by factors such as age, sex, genetics, physical activity, and nutrition.

Vitamin K2 is a crucial nutrient for bone health, as it activates (carboxylates) osteocalcin, a protein that binds calcium to the bone matrix. It also supports osteoblast activity and inhibits osteoclast-mediated bone resorption. Research has shown that children and adolescents have markedly high levels of inactive (uncarboxylated) osteocalcin, indicating low vitamin K2 intake. Addressing this deficiency through adequate nutrition or supplementation may optimize bone development during critical growth periods, improving peak bone mass and bone health later in life.

Bone development: The Basics

Endochondral Ossification

Bone development starts around the seventh week of gestation when mesenchymal stem cells differentiate into cartilage-producing cells [1], which form the framework or scaffolding for future bones. This cartilage is gradually replaced by bone in a process called endochondral ossification. Key steps include:

1. **Cartilage Framework Formation:**
   Specialized cells, chondroblasts, produce a cartilage model in the shape of the bone (Figure 1A).

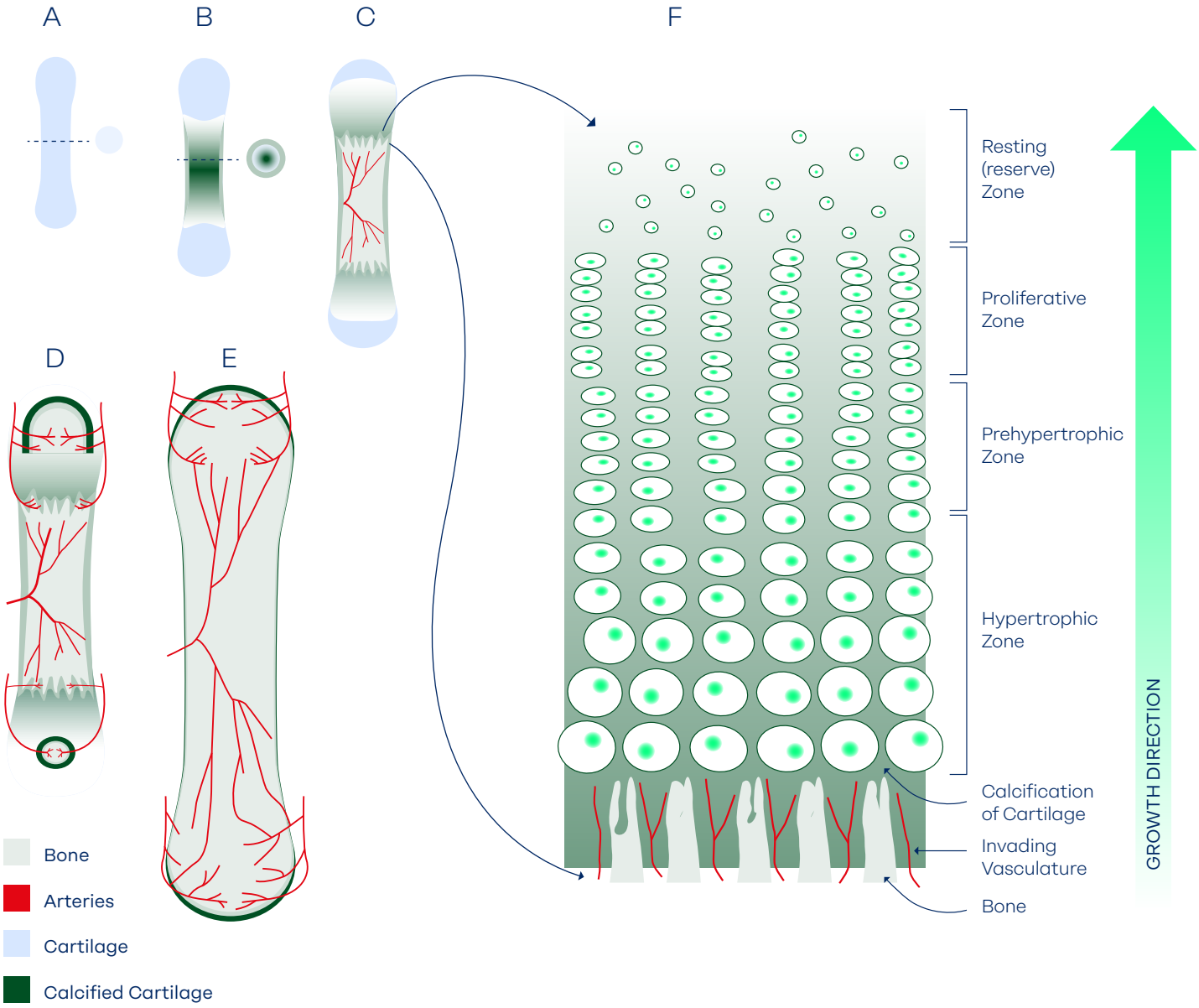
2. **Bone Collar Formation:**
   Some surface cartilage cells differentiate into osteoblasts which then begin creating a thin layer of bone around the midshaft region of cartilage like a collar [2]. The bone collar prevents nutrients from reaching underlying chondrocytes, which die and signal osteoclasts to punch holes in forming bone tissue to facilitate penetration of blood vessels [3] (Figure 1B).

3. **Vascular Invasion:**
   Blood vessels penetrate the cartilage, allowing for the formation of central bone marrow and the primary ossification center. For the long bones, vascular penetration at the ends leads to the formation of secondary ossification centers/growth plates (Figure 1C-E).

4. **Growth Plate Activity:**
   The growth plates, located at the ends of long bones, drive bone lengthening through cell proliferation, matrix production, and mineralization. Cells closest to the growth plate enlarge and produce large amounts of collagen. It is in this region, proximal to the growth plate that is vulnerable to nutrient deficiency resulting in chondrocyte death and transformation into a calcified cartilage zone where growth plate osteoblasts are recruited to mineralize and thereby lengthen bone by endochondral ossification (Figure 1F).

This process continues until late teens or early twenties, when the growth plates calcify and bones stop elongating [4].

Figure 1: Formation of bone by endochondral ossification

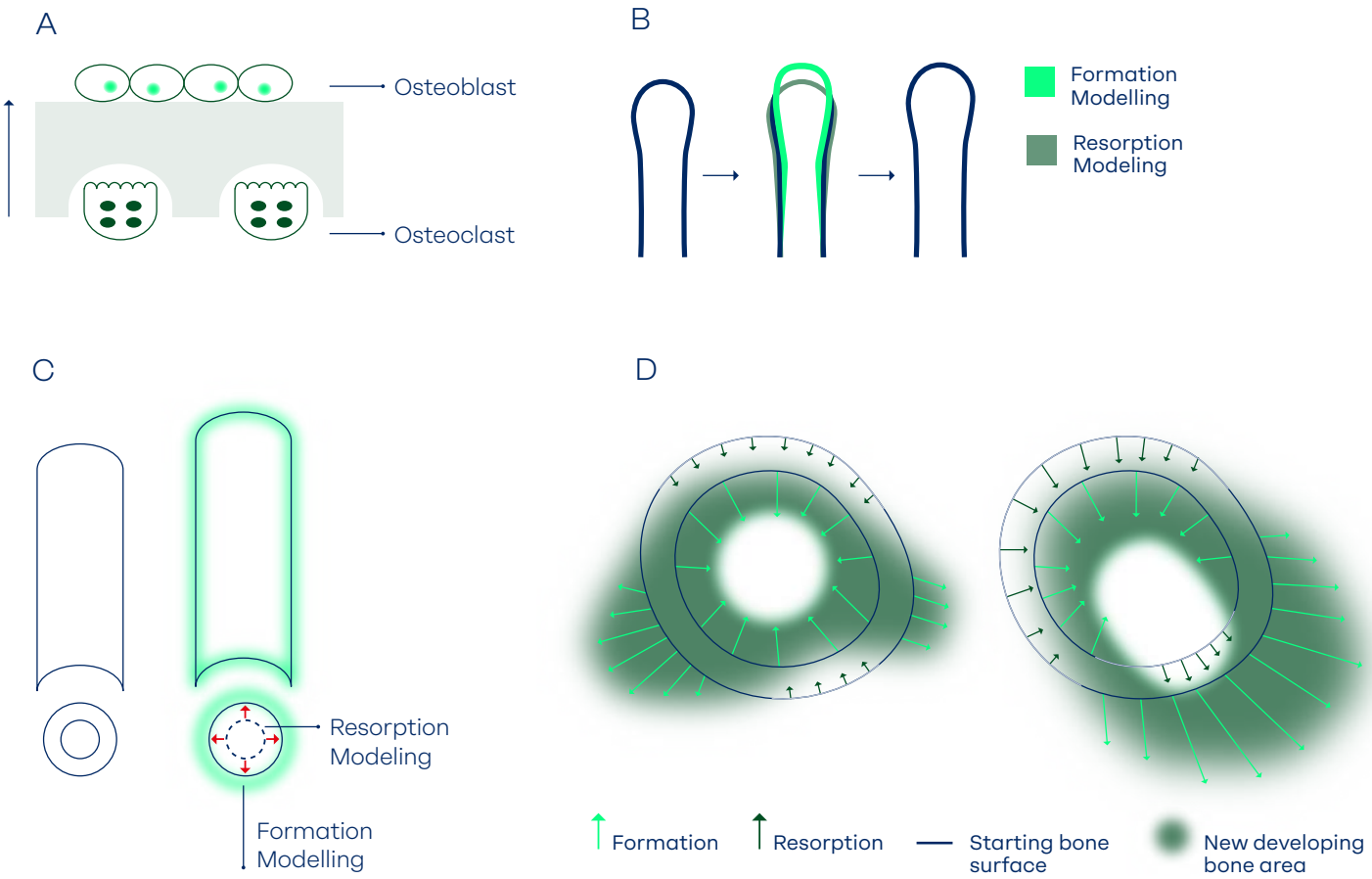


A cartilage framework starts the formation of bone (A), where some cartilage cells differentiate into osteoblasts which initiate a thin bone collar formation (B). Osteoclasts makes holes in the collar, allowing blood vessels to enter (C) for the formation of bone marrow and ossification centers (D-E). The lengthening of bone occurs at the growth plates and is driven by chondrocyte proliferation, matrix production, cell death and mineralization (F).

Bone Modeling

Bone modeling primarily occurs during childhood and adolescence to shape the skeleton and increase bone mass. This modeling is controlled by two independent mechanisms – bone formation by osteoblasts and bone resorption by osteoclasts. New bone is initiated by osteoblastic driven 'formation modeling' on the endocortical (or inner) surface of existing bone and bone is removed by osteoclastic 'resorptive modeling' on the periosteal (or outer) surface of bone in a tightly regulated manner to preserve bone shape [3, 4] (Figure 2A, B).

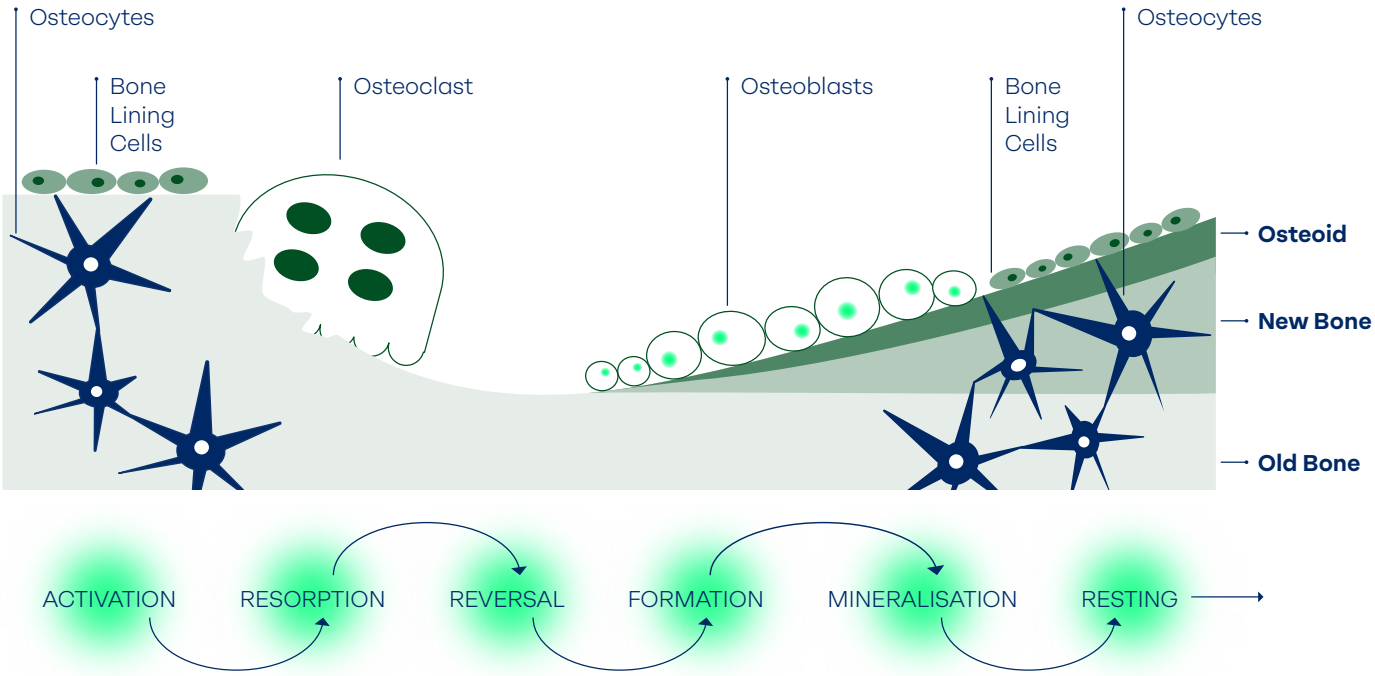
Figure 2: Bone modeling



Bone modeling is controlled by two independent mechanisms that occurs at different surfaces. Bone is formed by osteoblasts and resorbed by osteoclasts leading to a direction of growth (A). This mechanism gives a preservation of bone shape during growth (B), radial growth (C) and different shapes by bone drift (D).

Bones can also have radial growth which is a result of osteoblastic 'formation modeling' taking place on the periosteal surface and osteoclastic 'resorption modeling' on the endocortical surface (Figure 2C). This form of modeling is most prevalent during childhood and adolescence. Many forms of bone can be modeled by 'bone drift' which takes place primarily during growth, but can also be activated in later adult life, due to changes in mechanical loading of the skeleton. Bone drift is the consequence of formation and resorption taking place on different surfaces but also in a tightly coordinated manner to achieve different bone shapes (Figure 2D) [3, 4].

Figure 3: The Bone Modeling Cycle



Bone remodeling involves resorption and formation of bone at the same location. The process is initiated by microfracture in bone and microdamage of the network of osteocytes in bone. Some osteocytes will go into apoptosis and attract and activate osteoclasts. The bone lining cells will retract allowing resorption by osteoclasts. In the reversal stage, the osteoclasts leave the site, and loose collage is removed by lining cells. Osteoid rich in collagen and osteocalcin is formed by the osteoblasts allowing the formation and mineralization of new bone.

Bone Remodeling

Bone remodeling is a lifelong process that replaces old or damaged bone to maintain skeletal strength. Unlike modeling, remodeling involves the coordinated activity of osteoblasts and osteoclasts at the same location and occurs in a sequential order called the 'remodeling cycle'. In a healthy individual it takes about 4 to 6 weeks from the time osteoclasts are activated until the osteoblasts have completed their formation of the bone matrix. After the completion of the cycle, mineralization of the area will continue for more than a year (Figure 3) [3-5].

The remodeling cycle consists of five stages:

1. Activation:
This is triggered by bone microdamage to the network of osteocytes by which isolated osteoclasts die by apoptosis. This attracts osteocyte precursors to the microfracture site and coalesce to form active functional osteoclasts.

2.Resorption:
The cell lining covering mineralized matrix (or bone) retracts exposing bone to osteoclasts which then remove old or damaged bone and collagen and releasing minerals like calcium and phosphate into the circulation.

3.Reversal:
When sufficient bone is removed, osteoclasts leave the site and lining cells will further remove loose collagen and other fragments.

4.Formation:
Osteoblasts are now in a position to lay down new bone matrix, rich in collagen and osteocalcin, now called osteoid. Once this is complete, a slow mineralization with calcium and phosphate takes place with about 70% deposition within about 2 – 3 weeks. Full mineralization can take up to 1 year to be completed.

5.Resting:
When the rebuilding of the bone is competed, the lining epithelium once again covers the new bone and the bone enters a 'resting' phase, during which time mineralization can continue.

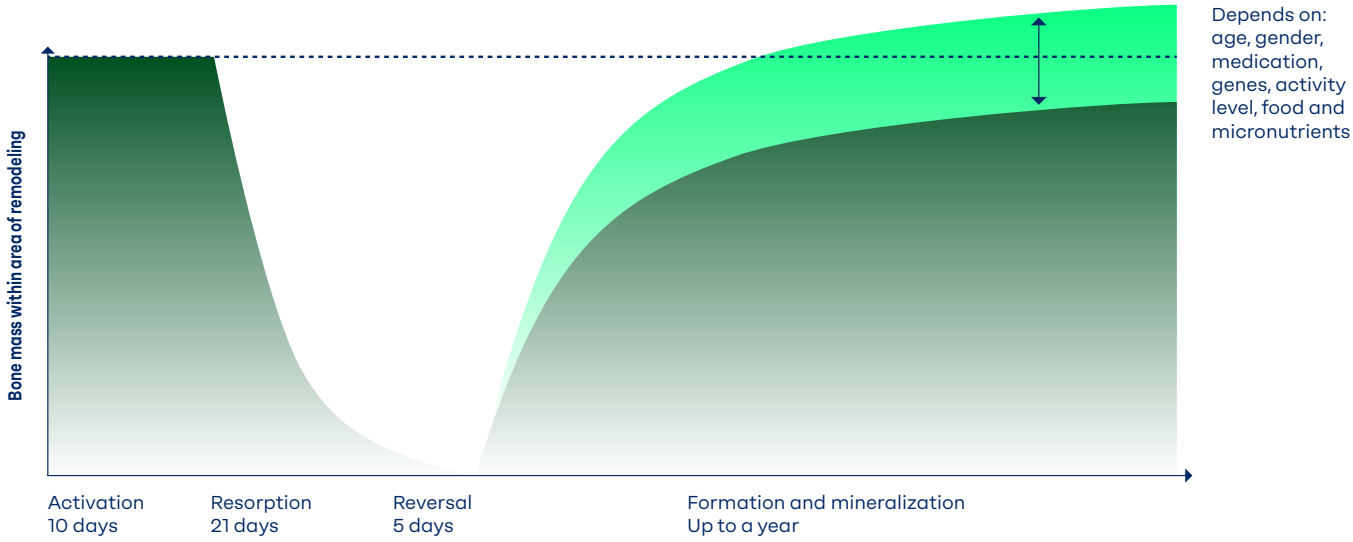
Activation lasts about 10 days, resorption about 21 days and reversal about 5 days. Bone formation typically last a year or even more.

Bone Remodeling Rate and Balance

The rate of bone remodeling is the highest during the growth phase and in terms of bone accumulation, results in an overall accretive outcome. Bone mass peaks in the late 20s to 30s and then begins to decline, as the balance shifts to more bone loss than deposition. This balance is dependent on several factors like age, gender, genes, medication, activity level, food and micronutrients (Figure 4) [3-5].

Key micronutrients that impact bone health are calcium, phosphate, magnesium, vitamin D, vitamin K2 and protein. Vitamin K2 downregulates osteoclast activity and promotes osteoblast activity. In addition, it acts as a cofactor for the carboxylation of osteocalcin, the biochemical mechanism responsible for bone mineralization. By acting on these three processes, vitamin K2 might shift the bone remodeling balance in favor of more bone [5].

Figure 4: Rate of Remodeling



The first stages in bone remodeling are relatively fast processes compared to formation and mineralization of bone. The rate of remodeling depends on many internal and external factors.

Vitamin K2

Vitamin K2 exists in several different forms in nature. All forms have the common ring structure menadione (2-methyl-napthoquinone) also known as menaquinones. At position 3, there is a poly-isoprenoid side chain attached, and each isoprenoid unit is unsaturated. The number of isoprenoid units varies which is the basis for classifying the different types of menaquinones (Figure 5A). They are named by their number of isoprenoid units in the side chain (MK-n, where n is the number of units). Different menaquinones are found in different foods. Short chain menaquinones, like MK-4, are found in dairy products like milk and butter. The long-chain menaquinones MK-7, MK-8 and MK-9 are found in fermented foods like cheese [6, 7].

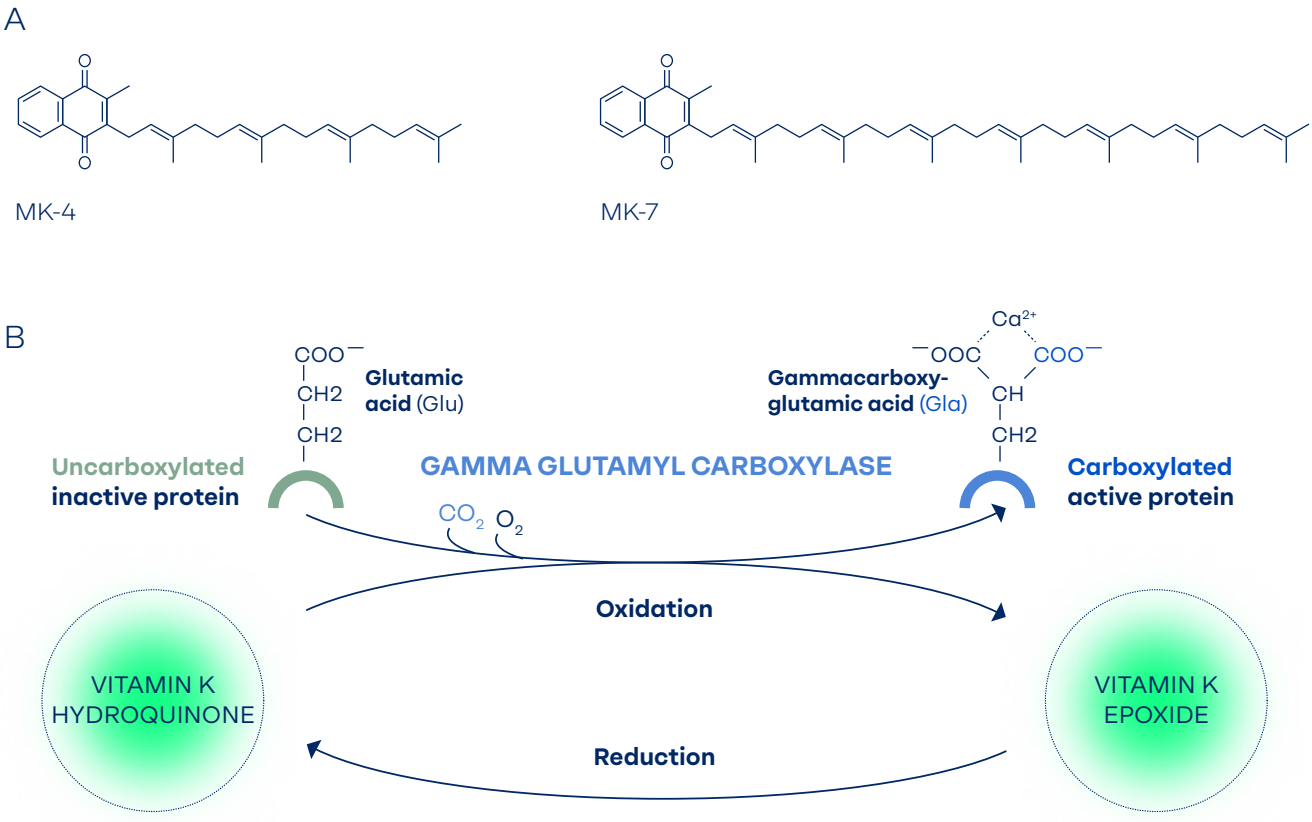
Vitamin K2 is one of the fat-soluble vitamins and is absorbed in the small intestine as micelles after being emulsified by bile salts. After being taken up by the lymphatic system, vitamin K2 enters the circulation as chylomicrons and taken up by the liver [8]. The different lengths of the isoprenoid side chains play a role in the lipophilicity of vitamin K2. The long chain menaquinones are transported by low-density-lipoproteins (LDL). The association of long chain menaquinones with LDL determines their activity in the periphery of the body where LDL receptors are expressed [7-9].

Mechanisms of Action

Vitamin K2 acts as a cofactor for γ-carboxylation of glutamic acid residues in vitamin K dependent proteins (VKDP). This is an enzymatic reaction driven by gamma-glutamyl carboxylase (GGCX), and together with vitamin K2, CO_2 and O_2, specific glutamic residues on the vitamin K dependent proteins are carboxylated to Gla residues. This post-translational modification changes the charge of these amino acids from one negative charge to two negative charges, something that allows interaction with calcium ions (Ca^{2+}) (Figure 5B). Today, there are 17 described members of the VKDP family. Several VKDPs have significant roles in mineralization via their interactions with calcium, like osteocalcin, matrix Gla protein (MGP), Gas6, GRP, periostin and periostin-like protein [10-12]. The action of these proteins is local within tissues and depends on the cells that express the protein and how they are distributed. Just as osteocalcin is expressed by osteoblasts and plays an important role the mineralization within bone [13], MGP that is expressed in smooth vascular muscle cells surrounding the vasculature where it is shown to inhibit the mineralization and accumulation of calcium deposits in the circulatory system [14]. In addition, several VKDPs are members of the coagulation machinery like prothrombin, factor VII, factor IX, factor X, protein C, protein S, protein Z. They are all important for the maintenance of a healthy of pro- and anti-coagulation within the blood stream.

Vitamin K2 also regulates several processes in the body that do not involve carboxylation. Studies have shown that vitamin K2 plays a role in many signaling cascades found inside cells. For vitamin K2, the most studied cascade is on the regulation of the nuclear factor kB (NFkB) signal transduction and its capacity to downregulate expression of small proinflammatory mediators like TNF-α, and interleukin-6 (IL-6) [15]. This has been documented in several trials, and a dose-response relationship has been established [16-18].

Figure 5: Vitamin K2 and the Vitamin K Cycle



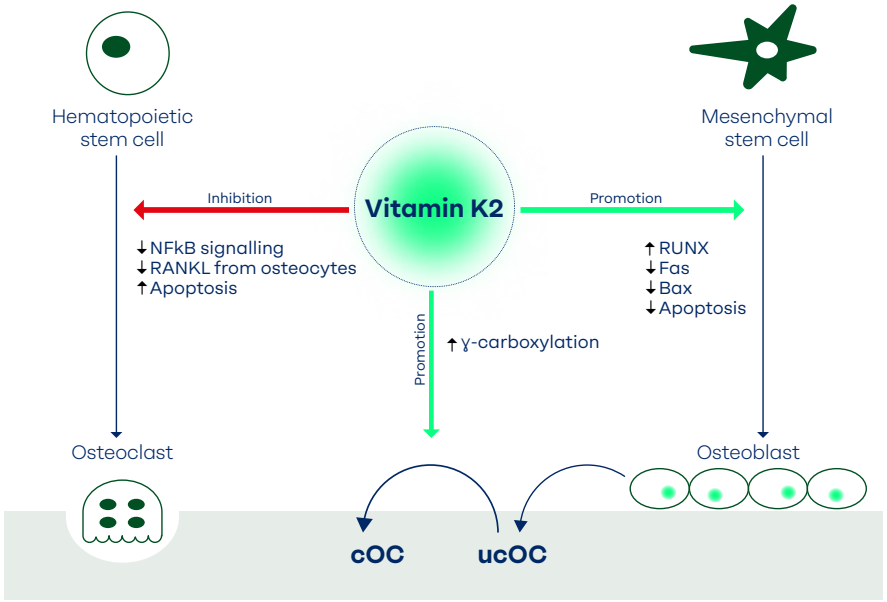
There are several forms of vitamin K2. The vitamers are defined by the number of isoprenoid units on the poly-isoprenoid side chain. Two examples are MK-4 which has four units and MK-7 which has seven units (A). Vitamin K2 acts as a cofactor for gamma glutamyl carboxylase. Specific amino acids (glutamic) in the vitamin K dependent proteins are carboxylated to Gla residues allowing interactions with Ca2+. In this process, vitamin K2 undergoes an oxidation into an inactive epoxide. Under normal conditions it is rapidly reduced to an active state as a hydroquinone. This cycling between a reduced and oxidated state is called the vitamin K cycle (B).

The Action of Vitamin K2 in Bone

The action by vitamin K2 on bone occurs in three ways; 1) carboxylation of osteocalcin, 2) promotion of osteoblasts, and 3) inhibition of osteoclasts [10] (Figure 6).

- **Osteocalcin** is highly expressed by osteoblasts and is the most abundant non-collagen protein in bone [19]. The protein has three ɣ-glutamic acid residues and carboxylated osteocalcin (cOC) colocalize with newly mineralized bone matrix [13]. It appears in the growing skeleton at the same time and location as the formation of hydroxyapatite [20-22]. Several clinical trials studying a variety of different populations have documented that intake of vitamin K2 can change the vitamin K2 status by increasing the level of cOC and lowering the level of ucOC [23-28].
- **Osteoblasts:** Vitamin K2 promotes osteoblast differentiation, enhances collagen production, and inhibits apoptosis. It achieves this by modulating pathways such as RUNX2 (runt-related transcription factor 2) and reducing the expression of pro-apoptotic genes like Fas and Bax [10, 29, 30].
- **Osteoclasts:** K2 suppresses osteoclast activity by downregulating RANKL (receptor activator of nuclear factor-κB ligand) expression and inhibiting NF-κB signaling. This reduces bone resorption and promotes osteoclast apoptosis [31, 32].

Figure 6: The Role of Vitamin K2 in Bone



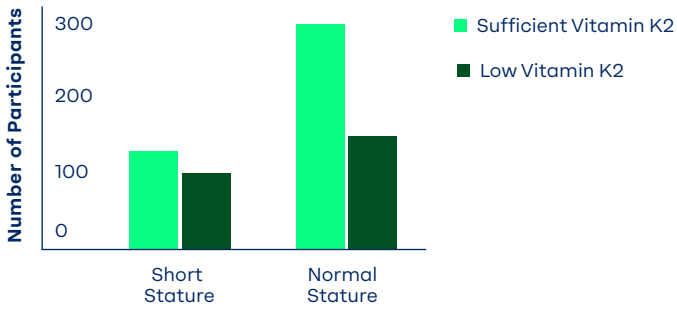
Vitamin K2 stimulates the differentiation from stem cells (mesenchymal origin) towards active osteoblasts. A biomarker for this transition is RUNX2 which is shown to increase in the presence of vitamin K2. The expression of two apoptotic genes (Fas and Bax) are downregulated by vitamin K2. Osteocalcin (OC) is highly expressed in osteoblasts and is secreted into the osteoid in the inactive/ uncarboxylated state. Vitamin K2 stimulates the activation to cOC. Osteoclast activity is inhibited by vitamin K2 via lowering of RANKL expression, inhibition of NFkB signalling and promotion of apoptosis.

Evidence of Low Vitamin K2 Status in Children

Low vitamin K2 status is associated with short stature

Growth is a complex process influenced by many factors. Lately, two studies have found that low vitamin K2 status is significantly associated with an increased likelihood of short stature in children. This has been shown in two cross-sectional correlation studies. In both trials the levels of vitamin K2 was measured in blood and they were significantly lower in children with short stature compared to children with normal height as well as a higher prevalence of vitamin K2 deficiency in shorter stature children [33, 34] (Figure 7 and Table 1).

Figure 7: Low Vitamin K2 Status

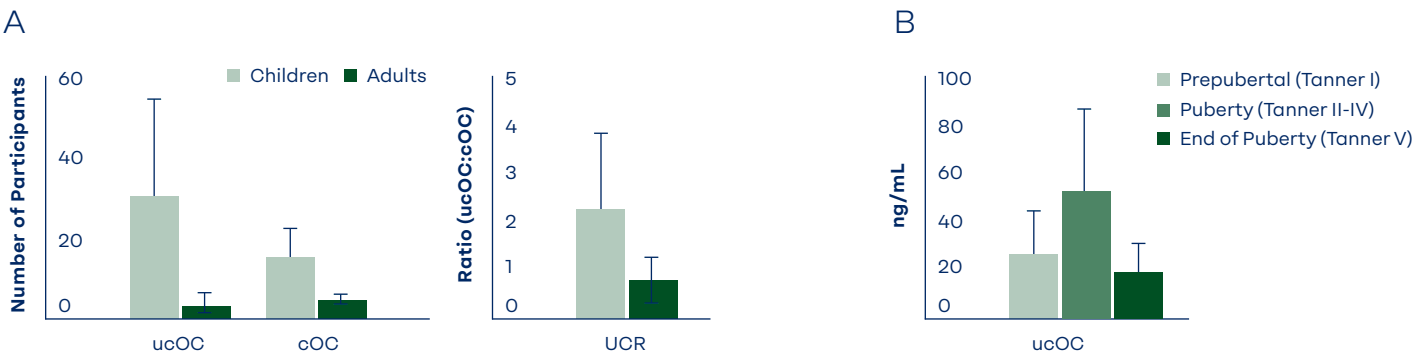


Two cross-sectional correlation trials documenting a link between blood level of vitamin K2 and height. Children with a short stature had lower levels of vitamin K2 when compared to normal stature children. Data is taken from [33].

Table 1: Overview of correlation studies where vitamin K2 deficiency or carboxylation of osteocalcin has been studied in children and adolescents

Reference	Population	Main findings
Van Summeren et al. 2007 [45]	86 healthy children between 3 and 18 yrs. 30 healthy adults between 25 and 35 yrs	Significantly higher levels of cOC and ucOC found in the children group compared to adults. The ratio ucOC/cOC was highest by end of puberty (Tanner V). ucOC was highest in mid puberty (Tanner II-IV).
O'Connor et al. 2007 [49]	223 girls between 10 and 11 yrs of age	High levels of ucOC correlated significantly with lower bone mineral content of the total body and lumbar spine
Van Summeren et al. 2008 [48]	307 healthy children between 8 and 14 yrs at inclusion	Improvements in the vitamin K2 status (by reductions in ucOC to cOC) was significantly associated with increased bone mass over two years.
Theuwissen et al. 2014 [47]	896 healthy children and adults. Children were 6-19 yrs of age, and adults were 20-80 yrs of age	The levels of ucOC were 6 times higher in children when compared to adults.
Paldanius et al. 2021 [46]	172 healthy children between 8 and 19 yrs of age	There was a peak in both total osteocalcin and cOC that coincided with the mid-pubertal stage (Tanner III-IV) for both boys and girls.
Shen et al. 2025 [34]	730 children aged 3-16 yrs of age	The prevalence of vitamin K2 deficiency was higher in children with short stature (80.6%) and near-short stature (64.7%) compared to those with normal stature (32.4%).
Chen et al. 2025 [33]	689 children aged 2-15 yrs of age	Children with short stature had significantly lower blood levels of vitamin K2 and a significantly higher prevalence of vitamin K2 deficiency. No association was found for blood levels of vitamin K1.

Figure 8: Low Vitamin K2 Status Measured by Osteocalcin in Children



The levels of both ucOC, cOC and UCR is much higher in children when compared to adults. The levels of ucOC is highest during puberty. Data is taken from [45].

High levels of inactive osteocalcin (ucOC) in children

Levels of osteocalcin are shown to be high in periods of life with high growth [35-39]. In a growing fetus, the osteocalcin levels increase from week 28 to week 35, and at birth they are up to 7 times higher than levels found in their mothers [40-42]. After birth there is a doubling of osteocalcin by 4 months of age. Bone quality during adolescence also seems to depend on the levels of osteocalcin in early life. A longitudinal trial showed that osteocalcin levels at 6 months of age were positively correlated with bone mineral content and density of the lumbar spine at the age of 17 years [43]. The high level of osteocalcin is regulated on a genetic level. Human osteoblasts derived from young donors expressed significantly more osteocalcin when compared to old donors [44].

There is more of both ucOC and cOC in children and adolescents when compared to adults, and the ucOC-to-cOC ratio (UCR) is higher in young populations. In 2007, van Summeren and colleagues studied the levels of cOC and the inactive form, ucOC, in a cohort of healthy children and adults in a cross-sectional correlation trial. In the childhood group, they found elevated levels of both forms of osteocalcin. Interestingly, they also found the UCR to be much higher in the children [45], (Figure 8A). The highest levels of ucOC were found in pubertal children (Tanner II-IV) (Figure 8B). In a Finnish cohort of healthy 7- to 19-year-old boys and girls, the peak value of cOC coincided with the mid-pubertal stage for both genders [46]. The level of the ucUC has been studied across different healthy age groups from 10 years to 70 years of age. When compared to the other age groups, the values of ucOC were more than 6 times higher among children and adolescents (up to 19 years of age) than adults [47].

A gain in vitamin K2 status correlates with gains in bone mineral content in children. This was shown in a longitudinal study with 307 healthy children followed over a period of two years. Both at baseline and after two years a high vitamin K2 status (measured by UCR) was associated with higher total body bone mineral content, and the relationship was most clear at the 2-years visit [48]. A relationship to bone quality has also been shown in 223 healthy girls with a mean age of 11 years where ucOC was inversely correlated to bone mineral content of the lumbar spine and the total body [49].

Since improvements in vitamin K2 status is associated with improvement in bone quality, it stands to reason that a low vitamin K2 status would have a negative impact on bone health in children and adolescents. The observed high prevalence of vitamin K2 insufficiency within this age group could be normalized with vitamin K2 supplementation, and an adequate level of vitamin K2 in the body may lead to improved bone quality and higher peak bone mass. With the transition from adolescence to adulthood, the body has the highest bone mass it will ever reach during its life. A high bone mineralization is shown to play a role on fracture risk. In healthy children, the rapid growth and increase in height is not accompanied by the same increase in bone mass and is shown to increase risk of fractures [50, 51]. Further, a high peak bone mass in late adolescence could prevent the development of osteomalacia and/or osteoporosis later in life [52, 53].

Supplementation of MK-7 in children

Supplementing MK-7 to children shows an effective uptake of the vitamin into the blood stream followed by carboxylation of osteocalcin and MGP. This is shown in healthy children between 6 and 10 years of age being supplemented with 45 µg/day of MK-7 (vs placebo) for 8 weeks [47, 54]. Table 2 gives an overview of clinical trials supplementing with MK-7 in children.

The dose of MK-7 to achieve an optimal carboxylation of osteocalcin in children is currently not known. Since children and adolescents have so much higher levels of ucOC this dose can be different from what has been administered to adults and therefore dose finding and intervention studies in children are needed to document effect on bone health.

Table 2: Clinical studies in children with vitamin K2 (MK-7)

Reference/Design	Population	Main findings
Van Summeren et al. 2009 [54], Double-blinded, placebo controlled clinical trial	55 healthy children between 6 and 10 yrs of age	Eight weeks supplementation of 45 µg MK-7 per day gave a reduction in ucOC (significant) and increase cOC (trend) when compared to placebo.
Ozdemir et al. 2013 [55], Open-label, single-arm clinical trial	20 children suffering from thalassemia major	One year supplementation of MK-7 (50 µg) and vitamin D (5 µg) per day improved bone mineral density and showed a trend for cOC increase.
Solmaz et al. 2021 [56], Randomized controlled clinical trial	29 children suffering from acute lymphoblastic leukemia between 1 and 17 yrs of age	The results suggest an early beneficial effect of the combination of MK-7 (100 µg) and vitamin D (10 µg) daily on bone mineral density in ALL patients especially during the period of steroid therapy in the first months.
El Borolossy et al. 2022 [57], Randomized controlled clinical trial	60 hemodialysis pediatric patients between 6 and 18 yrs of age	Four months supplementation of MK-7 (100 µg/d) and supplementation of MK-7 (100 µg/d) together with vitamin D (10 µg/d) gave a reduction in ucOC and dp-ucMGP.

Conclusion

Vitamin K2 is essential for bone development and maintenance, especially during periods of rapid growth. It supports bone mineralization, enhances osteoblast activity, and reduces bone resorption by osteoclasts. Ensuring sufficient intake of vitamin K2 during childhood and adolescence may improve bone quality, maximize peak bone mass, and support against osteomalacia, osteoporosis and potential fractures in later life.

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