All about hydroxyapatite with Anne O. Rice

Hydroxyapatite is a material of great interest in dentistry today due to its natural similarity to the mineral composition of human teeth and bones. It plays a significant role in remineralizing tooth enamel, helping to repair early cavities and strengthen teeth against decay. Unlike fluoride, hydroxyapatite directly integrates with enamel, filling microscopic defects and improving surface smoothness. It also offers biocompatibility, making it safe for patients, including children and those with fluoride sensitivities. Industry expert Anne O. Rice, BS, RDH, CDP, FAAOSH explores the history, benefits, and possibilities of hydroxyapatite in the following articles.

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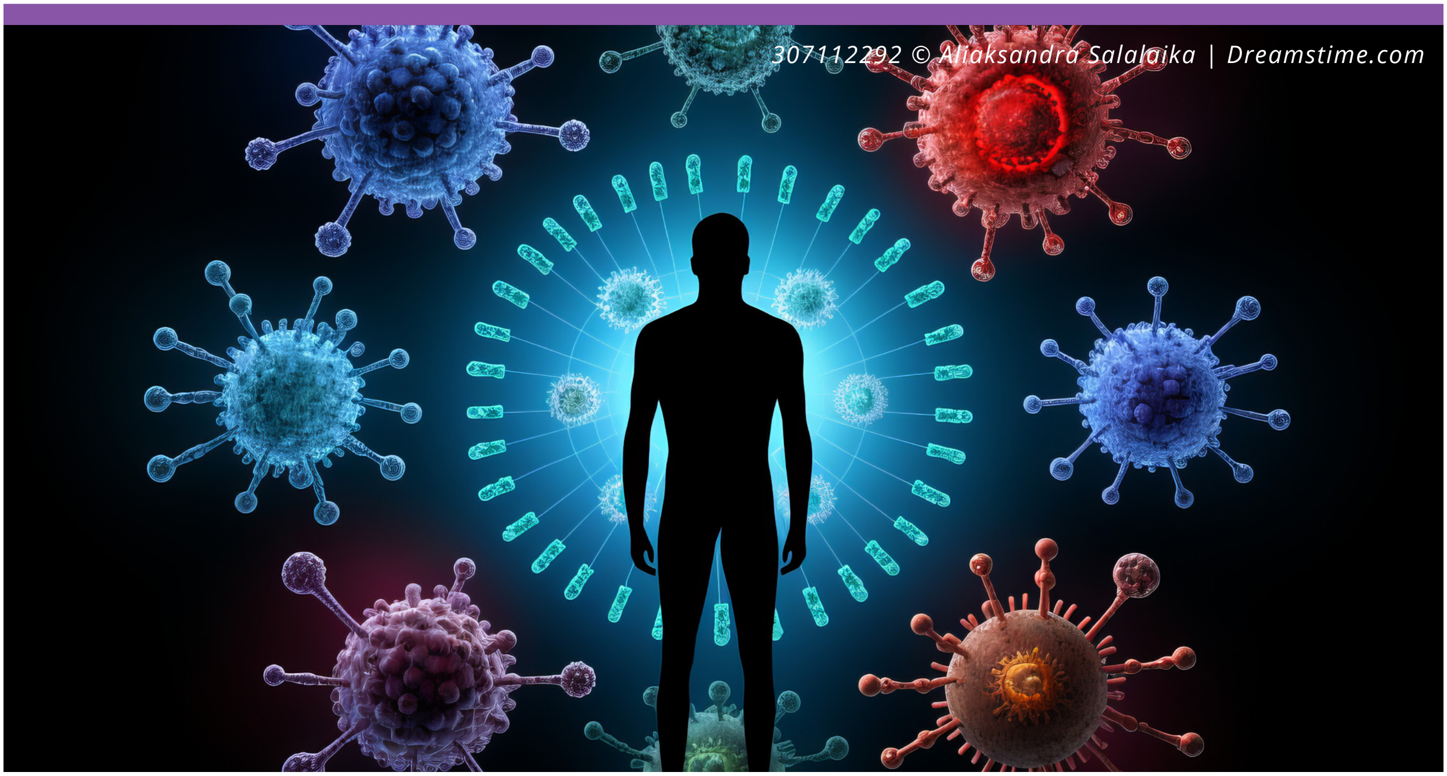
ABOUT ANNE O. RICE

Anne O. Rice, BS, RDH, CDP, FAAOSH, founded Oral Systemic Seminars after almost 30 years of clinical practice and is passionate about educating the community on modifiable risk factors for dementia and their relationship to dentistry. She is a certified dementia practitioner, a longevity specialist, a fellow with AAOSH, and has consulted for Weill Cornell Alzheimer's Prevention Clinic, FAU, and Atria Institute. Reach out to Anne at anneorice.com.

HYDROXYAPATITE AND THE IMMUNE SYSTEM

Understanding the mechanisms through which hydroxyapatite influences immune cell activity is crucial for developing advanced therapeutic strategies that enhance patient outcomes in regenerative medicine and orthopedic surgery.

ANNE O. RICE, BS, RDH, CDP, FAAOSH



The immune system is a complex network of cells, tissues, and organs that work together to defend the body against pathogens and foreign substances. This intricate system relies on various components, including innate and adaptive immune responses, to identify and eliminate threats. Among the many factors influencing immune function, biomaterials such as hydroxyapatite (HA) play a crucial role in modulating immune responses, particularly in bone health and tissue engineering.

HA is a naturally occurring mineral form of calcium apatite, primarily found in bone and teeth. Its chemical formula, $Ca_{10}(PO_4)_6(OH)_2$, closely resembles the mineral component of human bone. HA's biocompatibility, osteoconductivity, and bioactivity make it an essential material in orthopedics, dentistry, and regenerative medicine. When implanted into the body, hydroxyapatite interacts with the surrounding tissues, influencing cellular behaviors such as adhesion, proliferation, and differentiation.

Recent research has shown that hydroxyapatite not only serves as a scaffold for bone regeneration but also actively participates in modulating immune responses.[1,2] This interaction is critical for the success of biomaterials in clinical applications, as an appropriate immune response can enhance tissue integration and healing. Understanding the mechanisms through which hydroxyapatite influences immune cell activity is crucial for developing advanced therapeutic strategies that enhance patient outcomes in regenerative medicine and orthopedic surgery. By exploring the interactions between immune responses and hydroxyapatite, we can uncover the biomaterial's potential to modulate the immune system and promote tissue regeneration. This knowledge is essential for creating more effective treatments for bone-related diseases and injuries, ultimately improving healing and recovery processes.

INTERACTION WITH IMMUNE CELLS

The immune responses induced by hydroxyapatite (HA) particles can vary depending on size and morphology. Studies have shown that smaller particles, such as nanoscale hydroxyapatite (nHA), tend to have a stronger interaction with immune cells compared to larger, microscale particles.[3] This is because the size and shape of these particles influence how they are recognized and processed by the immune system. When HA particles are introduced into the body, they can be taken up by immune cells and nHA, due to their small size and high surface area, and are more readily engulfed by these cells, which can trigger a series of immune responses, including the activation of inflammatory pathways. Smaller HA particles may cause the release of pro-inflammatory cytokines, signaling molecules that help coordinate immune responses, while larger particles may provoke less of an inflammatory reaction.

nHA particles tend to have a higher surface-area-to-volume ratio, which can enhance their interaction with immune cells, such as macrophages and dendritic cells. Studies have shown that nHA particles can be more immunogenic compared to larger particles and may stimulate immune cells to release cytokines and chemokines, promoting an inflammatory response that can be beneficial in certain medical applications, as in bone regeneration, where controlled inflammation can promote tissue repair.[4] Microsized HA particles typically induce a milder immune response compared to their nanosized counterparts. Microsized particles range from 1 micron (μm) to 100 microns (μm) in diameter. A micron is one-millionth of a meter. Nanosized particles are typically between 1 nanometer (nm) and 100 nanometers (nm) in diameter. A nanometer is one-billionth of a meter, meaning that nanoparticles are significantly smaller than microsized particles. Microsized are less likely to be rapidly phagocytosed by immune cells, which may result in lower levels of inflammatory cytokine release. These larger particles are often considered less reactive in the immune system and are preferred in applications where minimal immune stimulation is desired, such as in long-term implants. Microsized is typically used in cosmetics since they aren't as small and are unable to penetrate past the skin's uppermost (epidermal) layers.

EFFECTS OF MORPHOLOGY

The morphology of HA particles—whether they are spherical, rod-shaped, or platelike—affects how immune cells interact with them. Rod-shaped HA particles have been shown to engage more actively with immune cells, potentially leading to greater immune activation because of how they are internalized by immune cells. Spherical particles are often less inflammatory than irregularly shaped particles. Irregular or needle-shaped HA particles can cause more irritation and lead to a stronger immune response, maybe because they are perceived as foreign by the immune system or cause mechanical stress on tissues. Platelike particles, on the other hand, tend to be more biocompatible and cause less immune reactivity, which might be advantageous for specific biomedical applications such as coatings on implants.

Nanosized particles are more readily phagocytosed and can induce a pro-inflammatory (M1) macrophage phenotype, leading to the release of cytokines such as IL-6, TNF-α, and IL-1β. These cytokines promote inflammation, which can be beneficial for bone healing but detrimental in other areas. HA particles can also influence the maturation of dendritic cells, which are crucial for initiating adaptive immune responses. When the cells encounter HA particles, they may become activated and present antigens to T-cells, leading to further immune activation. While most studies focus on the innate immune system, HA particles can indirectly affect adaptive immunity by modulating the activity of antigen-presenting cells (APCs) such as dendritic cells.[5]

EFFECTS ON THE IMMUNE SYSTEM

These interactions could have implications for long-term immune responses, especially in the framework of biomedical implants. Immunomodulatory properties of HA particles are particularly relevant in tissue engineering and bone repair. A moderate immune response, especially one involving M2 (anti-inflammatory) macrophages, can promote tissue regeneration and healing. Therefore, fine-tuning the size and shape of HA particles can enhance their therapeutic effectiveness.

Some studies have explored the use of nano-HA as a vaccine adjuvant, given its ability to enhance immune responses by promoting antigen uptake and stimulating innate immune pathways.[6] In 1993 it was reported that there was an antitumor effect of nHA on Ca-9 cells.[7] (The Ca-9 cell line is derived from human cervical carcinoma, which is a type of cancer that originates in the cervix.) Numerous studies have demonstrated that nHA has a significant killing effect on many kinds of tumors, such as melanoma, osteosarcoma, liver cancer, lung cancer, glioma, gastric cancer, and breast cancer.8-14 Most importantly, nHA has few side effects on normal tissue compared to the traditional chemotherapy drugs.

As much as there are benefits, there may be a potential for eliciting autoimmune responses. If nHA particles are perceived as foreign by the immune system, they could trigger an autoimmune reaction, wherein the body mistakenly attacks its own tissues. This risk highlights the importance of understanding how the immune system recognizes and responds to nHA and how modifications to the particle's surface may help mitigate this risk. The long-term effects of nHA on the immune system remain largely unexplored. Chronic exposure to nanoscale materials may lead to cumulative effects that could influence immune function over time. As nHA is used in various applications, such as coatings for dental implants or bone grafts, it is essential to assess the long-term biocompatibility and potential immunological impacts of these materials in vivo.

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HYDROXYAPATITE: ITS PAST AND FUTURE

Hydroxyapatite, a biocompatible substance that has been around for years, presents new possibilities for its use in dentistry.

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Hydroxyapatite, also known as hydroxylapatite (HA), is chemically represented as $Ca_5(PO_4)_3(OH)$, though it is commonly expressed as $Ca_{10}(PO_4)_6(OH)_2$, reflecting two entities forming the unit cell of the crystal. HA is naturally occurring and recognized for its impressive benefits in dental health, particularly in the remineralization of tooth enamel and dentin. HA aligns seamlessly with the body's natural processes, offering a biocompatible, effective alternative in oral care, with its bioactive, nontoxic, and osteoconductive properties enabling direct chemical bonds with living tissues. This mineral can be sourced from natural materials such as bone, marine organisms, plants, and phosphate rocks. Different manufacturing techniques today result in the production of various types of synthetic apatites.[1] Synthetic doesn't automatically mean something is bad. However, it *can* be slightly different than what is found naturally in the body. The synthetic production does allow for controlled purity, particle size, and other properties that can be tailored for specific uses.

HISTORY OF HYDROXYAPATITE

In the 1950s, the study of HA was largely centered on its chemical composition and structure, particularly its role as a major component of bone and teeth. This decade marked the beginning of more focused research into the material's potential biomedical applications, though it was still primarily in theoretical and experimental stages.

Through the 1970s, researchers observed that HA implanted in living organisms exhibited excellent biocompatibility and integrated well with surrounding bone tissue, sparking an interest in its use for bone grafts, orthopedics, and dentistry. Hydroxyapatite (HA) gained popularity as a bone graft substitute, serving as a scaffold for new bone growth, and its bioactivity and ability to integrate with bone made it valuable in dental implants, improving success rates. The use of HA became particularly prominent in bone repair and regeneration, especially for coating metallic implants. This enhanced the bone-implant interface and promoted better osseointegration.

During the 1980s and 1990s, synthetic HA was being developed to standardize it for broader use, allowing for controlled properties and the expansion of its use as a biomaterial. Concurrently, during the 1990s, researchers began exploring the use of nanoparticles as drug delivery systems. Nanoparticles have unique properties, such as a high surface-area-to-volume ratio, allowing them to effectively absorb, carry, and release therapeutic agents in a controlled and targeted manner. These systems were designed to improve drug stability, enhance bioavailability, and provide more controlled and localized drug delivery, reducing side effects. Since then, nanoparticle-based drug delivery has become a significant area of research in nanomedicine.

AN ALTERNATIVE TO FLUORIDE?

While fluoride has been the gold standard in cavity prevention and enamel support, there have been discussions about its overuse and potential toxicity that has led to a search for safer alternatives. "Biocompatible" means that the substance is readily accepted by the body and does not cause adverse reactions, which makes HA a particularly appealing option for individuals who are either sensitive to fluoride or prefer to avoid it due to health worries. It does not carry the risk of fluorosis, and it is nontoxic and safe for all age groups, including children. HA does help to remineralize initial carious lesions and has efficacy in biofilm control mainly through an antiadhesive property by which it can prevent bacteria from binding to the tooth surface.[2,3] HA has been shown to effectively reduce tooth sensitivity by forming a protective barrier over exposed dentin, a common occurrence due to erosion or recession.[4] The particles of hydroxyapatite penetrate the dentinal tubules and block them, preventing external stimuli from reaching the nerves. This protective layer not only reduces sensitivity but also aids in the healing process of the dentin itself.[5]

DOES SIZE MATTER?

Is nano-hydroxyapatite (nHA) better? When people speak about nHA and HA, they often use the terms interchangeably. Although nHA and HA are chemically and structurally similar, there are key differences that lie in their surface area. nHA (20-100 nm in diameter) consists of numerous tiny crystals, giving it a much larger surface area compared to the single large crystal structure of standard hydroxyapatite (larger than 1 micron). nHA is much closer in size to the apatite crystals found in tooth enamel, and the increased surface area enhances this bioactivity and reactivity, making it more effective in processes such as remineralization and bone regeneration.[6,7] Micro-HA is about 5-10 microns in size, which is larger than enamel HA and dentinal tubules, making it less effective for reduction in sensitivity and caries management.

In the 1970s, NASA played a significant role in nHA research and application by helping astronauts maintain teeth and bones while they were in space. Eventually, a Japanese company obtained the patent from NASA, and in the early 2000s, the company Sangi Co. figured out how to make the nanoparticles even smaller, leading to where we are today.

HYDROXYAPATITE IN DENTAL PRODUCTS

The use of nHA in toothpaste and mouthwash has gained popularity, but there are potential risks associated with nanomaterials. Nano-sized particles have the potential to penetrate deeper into tissues compared to larger particles. This raises questions about whether nHA in toothpaste and mouthwash could be absorbed by the gums or oral mucosa and enter the bloodstream, where they might interact with other organs. Current studies suggest that nHA is too large to be absorbed systemically through the oral tissues and is primarily eliminated through saliva.[8,9] Nanoparticles, in general, are scrutinized because their small size allows them to interact with biological systems in unique ways, and there is apprehension about their long-term safety, particularly regarding their ability to induce oxidative stress or disrupt cellular functions. Most research has not shown significant toxicity related to nHA at the concentrations typically used in dental care products.

There has been a query of aerosolization of nHA particles in mouthwash, or toothpaste when brushing, leading to inhalation of the particles. Nanoparticles can potentially enter the lungs, leading to respiratory fears, because inhalation of fine particles is generally considered a risk for lung health. This risk is considered low in nHA, especially with toothpaste, where the particles are contained in a paste and less likely to become airborne. However, with mouthwash or spray products that might aerosolize nHA, there could be a small but not well-researched risk of inhalation.

The use of nanoparticles, including nHAP, may raise environmental unease. After use, particles can enter wastewater systems, and the long-term impact of nanomaterials on the environment, including their persistence and potential to accumulate in ecosystems, is still under investigation. While the individual impact from personal care products such as toothpaste and mouthwash might be small, the cumulative environmental load from widespread use of nanomaterials is a growing area of study.

There are significant concerns regarding the morphology of HA particles. The shape can vary considerably based on the synthesis method used. Depending on the preparation technique, a wide range of particle shapes and sizes can be produced, from needles and spheres to platelets, exhibiting varying surface roughness and smoothness. Different morphologies can influence the behavior of HA in biological systems, including its interaction with cells and tissues. For example, needlelike and rod-shaped particles may exhibit different cellular responses compared to spherical particles, which can affect their applications in biomedical fields. Regulatory agencies such as the European Commission's Scientific Committee on Consumer Safety (SCCS) and the US Food and Drug Administration (FDA) tend to be cautious about the use of needle-shaped nanoparticles in consumer products, including toothpaste, because of potential risks associated with their shape and ability to penetrate biological tissues. When speaking with Jason Nesta, a cosmetic chemist, he mentioned that "needle-shaped nHAP particles are not allowed to be used in toothpaste (or any cosmetic products)" and has "read some studies that conclude needle-shaped nHAP causes inflammation, so I presume that is not very commonly used in any health-care applications either." Since toothpaste is applied topically and not implanted into tissues, the immune response would inherently be less of an issue. The oral environment typically does not lead to the same systemic immune reactions that might occur with internal medical uses of HA.

The most prominent nHAP that is used in toothpaste is called nano-XIM and is supplied by a company called Fluidnova. They provided all the safety studies to the European Scientific Committee on Consumer Safety (SCCS), and the SCCS concluded that rod-shaped nHAP like what Fluidnova makes is safe for use in toothpaste and mouthwash. Another large manufacturer, Sangi in Japan, makes medical grade HAP and was approved by the Japanese government as an anticaries agent.

MORE RESEARCH NEEDED

While research indicates that hydroxyapatite is generally safe, conclusive evidence is still lacking. In cosmetics, the hydroxyapatite used is typically microsized, much larger than nano-sized particles and cannot penetrate beyond the uppermost layers of the skin (the epidermis). It functions as a soft shell that gradually breaks down to release beneficial content. The SCCS has evaluated hydroxyapatite (nano) and considers it safe for use at concentrations of up to 10% in toothpaste and up to 0.465% in mouthwash. However, this safety assessment applies specifically to nHA with the following characteristics: it must be composed of rod-shaped particles, with at least 95.8% having an aspect ratio of less than 3 and the remaining 4.2% having an aspect ratio not exceeding 4.9; the particles should also be uncoated and not surface modified. In some regions, such as Japan and parts of Europe, nHA has been used in dental products for years without significant safety issues. However, in other areas, regulatory bodies are still assessing the long-term safety and effects of nanoparticles in consumer products. The SCCS's final opinion emphasizes that only rod-shaped particles are deemed safe for use in toothpaste, highlighting one of hydroxyapatite's most significant benefits: its ability to aid in the remineralization of tooth enamel. Hydroxyapatite is FDA approved for medical applications, but not yet dental. The truth is, many oral care ingredients, including fluoride (yes, fluoride!), lack FDA approval for certain uses, and we use them off-label. This doesn't mean fluoride or hydroxyapatite don't work—instead, it highlights the evolving landscape of oral health research and regulation.

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THE SYNERGISTIC POWER OF NANO-HYDROXYAPATITE AND VITAMINS FOR ORAL HEALTH

As clinicians, we have the opportunity to prevent oral disease and promote oral and systemic wellness. Here's a look at how nano-hydroxyapatite can work with vitamins to build and maintain children's dentition.

ANNE O. RICE, BS, RDH, CDP, FAAOSH

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In honor of Children's Dental Health Month, we celebrate the younger folks and the opportunities for prevention we have as clinicians. Here's a look at how using vitamins along with a mineral, nano-hydroxyapatite, can help build and maintain children's dentition.

THE ROLE OF VITAMIN D

To be clear, vitamin D is not a vitamin; it's considered a hormone and is responsible for increasing absorption of calcium, magnesium, and phosphate. Vitamin D3, or cholecalciferol, is a type of vitamin D made by the skin through sunlight exposure. Vitamin D2, or calciferol, can be gotten from plants but is less effective than D3 for raising blood levels of D.

Vitamin D is necessary for several bodily functions, including management of calcium levels, supporting healthy bones and immune systems, reducing inflammation, and glucose metabolism. Vitamin D and calcium are needed for muscle movement and nerve communication, and those sunlight beams help support sleep and may protect against type 1 diabetes, multiple sclerosis, and several forms of cancer.[1]

THE ROLE OF SUNLIGHT

Sunlight is the bright shiny object for health. It begins the process of producing vitamin D in the body. When UVB rays hit the skin, they interact with a protein, 7-dehydrocholesterol (DHC), helping to produce vitamin D3. Unfortunately, the increase of time spent indoors, whether due to lifestyle or work, along with protection of the skin from sun damage, creates a deficiency in the amount of sunlight that is needed for the vitamin process.

THE ROLE OF DIET

Diet is always important for health and wellness, but its contribution is small in the building of D3. Supplementation is recommended by many doctors for patients who have tested low or are at risk. Higher risk individuals may be those who are homebound, older, with dark skin pigmentation, obese, have digestive issues, and people on certain medications that interfere with vitamin D metabolism.[2,3] Forty to sixty percent of the US population is vitamin D deficient, including pregnant women.[4] Hopefully, obstetricians mention to their patients how important D3 is for not only reducing pregnancy complications but also for building babies' bones and teeth.[5]

THE RELATIONSHIP BETWEEN VITAMIN D AND CALCIUM

Vitamin D plays an important role in helping our bodies absorb calcium from the intestines. If a child doesn't get enough vitamin D, it doesn't matter how much calcium they eat; their body won't be able to use it properly for healthy bones.

How do we get children more vitamin D? Without sunlight exposure, parents can try the vitamin D food route. Fatty fish, cod liver oil, wild caught salmon, canned sardines, fresh shiitake mushrooms, and egg yolks all contain vitamin D. However, many of these foods are not favorites of small children. Foods such as milk, orange juice, infant formula, yogurt, butter, cheese, and breakfast cereals are often fortified with vitamin D, which helps tremendously.

VITAMIN D AND DENTAL CARIES

Dental health can be compromised with a deficiency in vitamin D for the young and old alike. The body manages minerals through a calcium balance and the immune system, which are both regulated by vitamin D.[6] Research has shown a 49% decrease in decay among people who took vitamin D3, and children with severe childhood cavities had much lower vitamin D levels than children without.[7,8]

VITAMIN K AND DENTAL HEALTH

Let's not forget vitamin D's friend, vitamin K, a fat-soluble vitamin discovered in 1929 that has two types. The original discovery was named *koagulationsvitamin* from the German word for coagulation, since the vitamin has essential blood clotting properties. We now call it K1, and it is found in green leafy vegetables such as spinach and kale.

K2 has 10 subtypes and lasts longer than K1. It is found in animal and fermented foods such as natto, sauerkraut, and some cheeses, and can be produced by gut bacteria in the large intestine. People with gastrointestinal disorders and chronic diseases, such as celiac, ulcerative colitis, and cystic fibrosis, may not absorb vitamin K properly.

CALCIUM ABSORPTION AND VITAMINS

K2 is proving to be as important as vitamin D for dental health, but we still have a lot to learn. Although vitamin D is needed for adequate calcium absorption, vitamin K2 directs the calcium to the skeleton to prevent the calcium from being deposited in the wrong areas.

If calcium is taken in isolation without other nutrients such as magnesium, vitamin D, and vitamin K, it can lead to the buildup of plaque in coronary arteries. A 2008 study showed that improving vitamin K status in children over a two-year period resulted in stronger and denser bones.[9]

In the last five decades, vitamin K2 intake among parents and their children has decreased significantly. Low vitamin K status is much more frequent in newborns due to both endogenous and exogenous insufficiencies.[10] An ongoing clinical trial is testing whether vitamin D3 and K2 supplementation might positively influence the biological process of bone healing.

ORAL HEALTH RECOMMENDATIONS

Setting the stage for a lifetime of good oral health begins with the development of teeth. This is an area where we can counsel expectant mothers, helping their babies develop strong bones, strong teeth, and strong health.

An adult supplement with a D3 and K2 combo may help pull calcium out of circulation and into bones. For children, an oral supplement may be difficult, but dentistry has come a long way in helping them have strong, healthy dentitions. Product options are growing by leaps and bounds for lowering decay risk and building solid foundations. Nano-hydroxyapatite or xylitol added to products in our home-care routines can make a difference.

Keep the science in mind when trying out new products. Nano-hydroxyapatite is an expensive ingredient and if not included in a product at an adequate level the efficacy may be compromised.

Nano-hydroxyapatite is a calcium phosphate, and vitamin D helps the digestive system absorb the calcium. Add K2, which helps activate the proteins needed to take the calcium into the teeth and bones, and you have a great combo.

New and natural alternatives provide more options not only for adults but also for children's oral health. The elimination of sodium lauryl sulfate, artificial sweeteners and flavors, and preservatives gives parents more choices, but products must work, scientifically. Understanding the route of calcium into our teeth and bones is one piece of the puzzle when making recommendations to parents.

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