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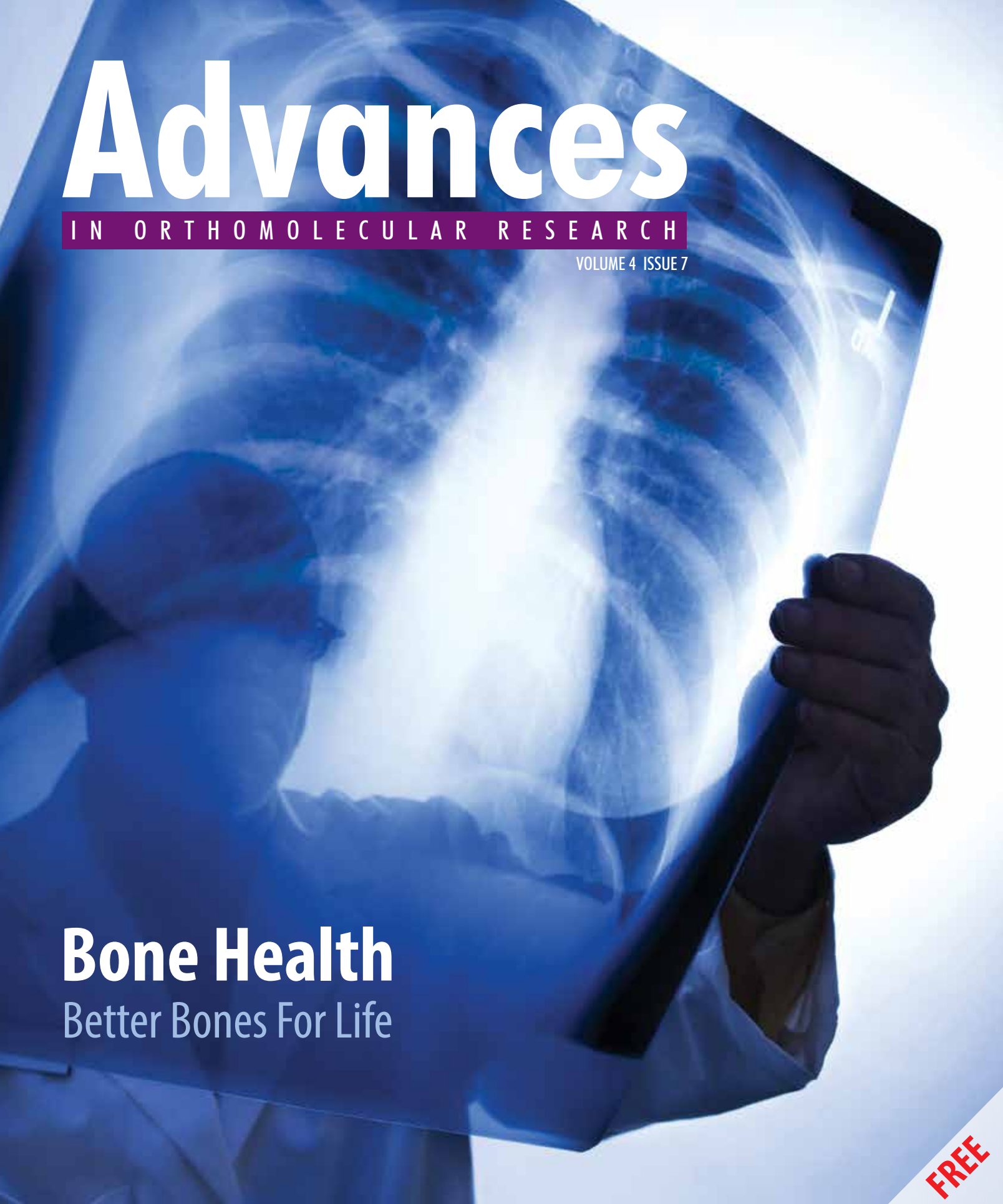

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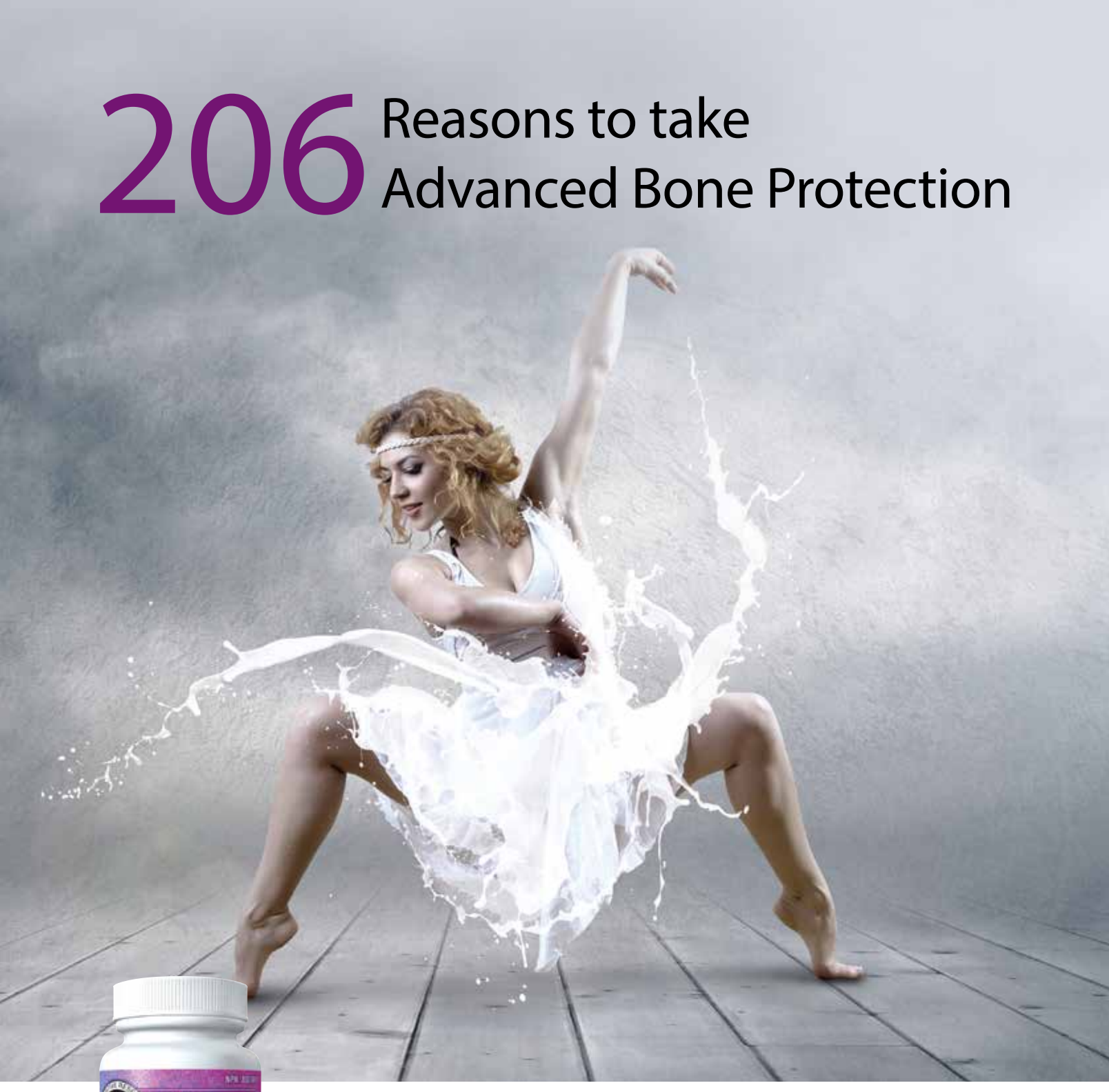

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ADVANCED ORTHOMOLECULAR RESEARCH

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ADVANCED ORTHOMOLECULAR RESEARCH

Skeletal Development and its Influential Factors

A typical adult human skeleton consists of 206 bones. The skeleton gives support to the body and acts as a reservoir of various minerals. In spite of its solid appearance, the bone constitutes a very dynamic tissue that undergoes a continuous process of formation and resorption. The complex molecular mechanisms regulating bone remodeling are not fully understood, but we know that it involves a crosstalk between two types of cells: bone breakdown and resorption cells called osteoclasts and cells that form bone called osteoblasts. Osteoclasts degrade the mineral matrix in response to a variety of signals, while osteoblasts deposit new matrix at the resorption sites. This delicate balance varies during the body's development stages: in children and adolescents, the rate of formation of bone mineral predominates over the rate of resorption, while in later life, the resorption predominates. A gradual loss of bone density accompanies the normal aging process and in certain cases, it gives rise to age-related bone diseases such as osteoporosis.

The Process of Building Bones

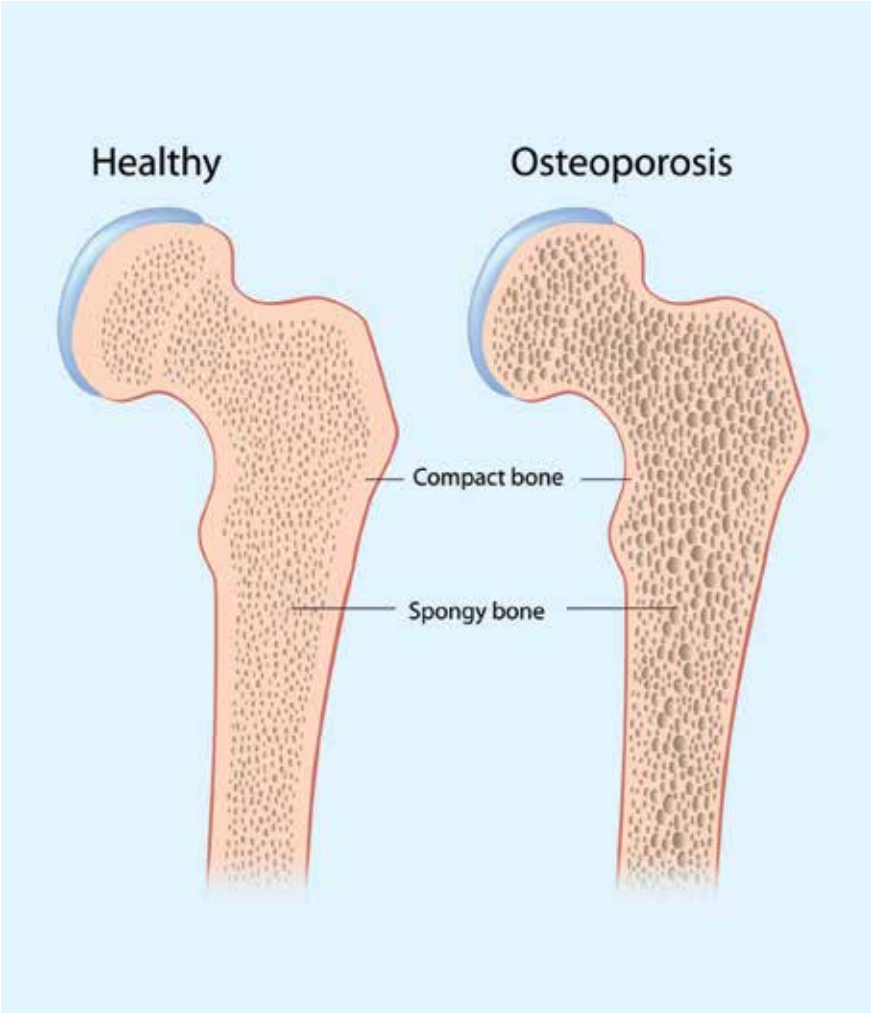
Many factors affect the rate and extent of bone remodeling, including mechanical stress and hormonal imbalances. Extracellular calcium is one of the main factors regulating this process. Calcium is involved in the recruitment and activation of osteoclasts and their subsequent detachment from bone. The systemic mechanism regulating calcium availability, storage and disposal is regulated by parathyroid hormone (PTH) and vitamin D. The bone remodeling process is also under the influence of other hormones (calcitonin, oestrogens and glucocorticoids), messenger proteins called cytokines and bone matrix-embedded factors.

Normally, the level of calcium in the blood is carefully controlled. By means of a feedback loop, concentrations of extracellular calcium are kept balanced. The parathyroid glands respond to low levels of calcium (hypocalcemia) by secretion of PTH. PTH, in turn, stimulates the liver conversion of

vitamin D3 to its active form. PTH and vitamin D3 act on calcium homeostasis by stimulating its retention in the kidney and intestines. Both hormones also increase circulating calcium by promoting the formation of new osteoclast cells which release calcium from the bones. When the blood concentration of calcium reaches a certain level, the negative feedback interrupts the secretion of PTH and the production of active vitamin D3. When the calcium concentration rises too high (hypercalcemia), the process is reversed: calcium excretion is increased and the bone resorption from increased osteoclast activity is slowed down.

Bone development is a never-ending process, initiated during fetal growth and lasting throughout adulthood and old age. And despite the notion that milk is the best thing around for building healthy bones, the story is much more complex than that. In fact, a new study actually found that drinking milk in adolescent years has no impact on fracture rates in adulthood![1] So, if milk isn't the answer for healthy bones, then what is?

Let's take a look at the developmental process, the physiological importance of our skeletal system and the many factors that affect the health of our bones.



How Do Bones Grow?

The human body contains 206 adult bones and the development process is quite complex, as one could imagine. We are actually born with a very small amount of "bone" tissue and, instead, a great amount of soft cartilage. As we grow into adulthood, the body must transform this cartilage into bone through a highly regulated system called endochondral ossification.[2]

On a cellular level, three important cell types have been identified: osteocytes, osteoblasts and osteoclasts (see Key Terms). Now, all of these different cell types are always present and active in the body but, depending on the stage of growth and location of the bone, certain cells are more active than others. By examining their activity, we can divide the bone development process into the two distinct categories of modeling and remodeling.

Bone modeling is implemented during our infant, childhood and adolescent years and it involves elongation and physical increases in the size of our bones.[3] This process requires a higher rate of osteoblastic activity at the site of growth plates, where endochondreal ossification actually takes place. Ultimately, modeling is highly regulated by hormones that stimulate the growth of many tissues such as sex hormones (estrogen and testosterone), growth hormone (GH), thyrotropin and insulin-like growth factor 1 (IGF-1).[3]

Once a bone is fully ossified and formed, it enters the constant state of readjustments called remodeling. Essentially, remodeling consists of a constant replacement of old bone cells with new osteocytes to keep them strong and healthy.[3] In this scenario, osteoclastic activity and osteoblastic activity are balanced.

Generally speaking, we want predominantly osteoblastic activity or at least a balanced activity of osteoclasts and osteoblasts. In the cases of osteopenia and osteoporosis, osteoclastic activity predominates, thereby leading to a decreased bone mineral density (BMD) and higher risk of fractures.

What Do Bones Do For Us?

Our bones are involved in much more than simply forming our physical structure. Sure, they give us shape, but they are still an organ system. And any organ interacts with the rest of our body through multiple mechanisms. What follows are some of the skeletal system's key functions.

Movement: Although our muscles allow us to move, they are only a part of the equation. Bones act as anchor points for muscle attachments. In turn, when muscles contract then they are pulling on bones, allowing for movement.

Mineral Balance: The calcium and phosphorus within our bones actually act as a reservoir for our body to maintain acid-base equilibrium. The ability to keep a balanced acidity level is so important that our bodies will sacrifice bone health to do so. In fact, up to 15% of skeletal calcium can be lost over a decade to buffer a mild metabolic acidosis due to acidic dietary practices![4]

Organ Protection: Many people overlook the fact that our bones are designed as a shield and a form of armor for our vital organs such as our brain, lungs and heart. A stronger set of armor makes for a better defense against injury!

Blood Cell Manufacturing: Bone contains bone marrow, a manufacturing facility for red blood cells, white blood cells and platelets. This means that we need our bones to form our immune system and regulate the cells responsible for oxygen and nutrient delivery.[5]

Hormone Balance: Components of bone have been shown to exhibit a hormonal impact on multiple organ systems. For example, osteocalcin found in the bone tissue is now known to regulate energy expenditure through fat deposition and insulin secretion.[3] What is perhaps even more impressive is that osteoblasts have been found to stimulate testosterone production by the testis in males.[3]

Why Do Our Bones Breakdown?

Poor Diet: First and foremost, building healthy bones involves much more than just getting enough calcium and vitamin D. This is evident by the aforementioned study on milk and fracture risk! Although these nutrients are crucial for bone mineral density, a wide variety of vitamins and minerals are needed to develop optimal bone structure and function.[6,7] Bones are at a greater risk of breakdown when *any* of these are deficient, collectively or in some combination.

By reviewing the various mechanisms that different nutrients play in relation to the skeleton, it is easy to see that they all interact and work synergistically to create healthy bones. On the whole, the dietary emphasis needs to change from calcium sources to whole foods including green leafy vegetables, nuts, seeds, legumes (i.e. beans) and whole grains.[6] This combination of foods will specifically provide the aforementioned minerals and vitamins important for your skeletal system. Even green tea, rich in bioflavonoids such as epigallocatechin gallate (ECGC), has shown a positive impact on BMD – so drink up![8]

Hormonal Imbalances: Many hormones are involved in regulating bone mineral density, and estrogen is often cited as the prime example. It has long been known that the estrogen deficiency that accompanies menopause is a major contributing factor for osteoporosis. This should be of no surprise when we consider that estrogen receptors are actually found on the surface of osteoclasts, osteoblasts and osteocytes[9], and so their activation (or lack of) will dictate how each set of cells behaves. In addition, estrogen deficiency has been shown to increase oxidative stress and have a pro-inflammatory effect in the body.[9]

Although estrogen is considered the most important sex hormone to influence bone health, the roles of progesterone and testosterone cannot be overlooked. In fact, a study in perimenopasual women suggests that higher progesterone levels might be associated with more bone formation and less bone resorption.[10] Treatment with testosterone replacement in middle-aged men has been shown to reduce bone resorption markers and improve BMD in the lumbar spine.[11] Clearly, the hormonal component of bone health cannot be undervalued and more work must be done to better understand how all of these sex hormones work together for proper skeletal protection.

Lastly, cortisol (a hormone released from our adrenal organs when under

stress) plays a monumental role in bone development. Chronic stress and elevated cortisol leads to an increased rate of bone turnover, impaired absorption of calcium and inhibition of sex hormones![12] This is evident by the increased incidence of osteoporosis and fractures in those with Cushing's syndrome (a disease of consistent excess cortisol output). What is more concerning is that even if cortisol is within a normal range in women as young as age 19-35, a negative association between cortisol and BMD has been observed.[12] Overall, this highlights the importance of regular stress management and stress coping techniques throughout life.

Inadequate Sleep: In our previous issue of Advances (Stress Part II), we detailed the importance of sleep and briefly mentioned its impact on healthy bones. Numerous studies have demonstrated that irregular sleep patterns may have detrimental impacts on bone health. One study in over 600 Chinese women found that shorter sleep duration was associated with decreased total BMD in those over the age of 45.[13] Specifically, significant impairments in bone health were seen in those women sleeping less than 6 hours per night.

The corresponding decreased BMD in those with less sleep is most likely due to the resultant elevations in cortisol during the daytime.[13] In other words, stress can cause sleep deprivation and sleep deprivation can cause stress. This forms a vicious cycle of elevated cortisol that suppresses bone marrow cell production and triggers osteoclasts.[13] Increased inflammation via activation of proinflammatory cells is a compounding problem that develops as a result of sleep deprivation.[14] To prevent this destructive process, it's imperative to get 7-8 hours of sleep per night on a consistent basis!

Lack of Exercise: Weight bearing exercise has long been known to contribute to strong bones by inducing a strain on the tissue. As the bone is stressed, mechanoreceptors and hormones are activated to induce osteoblastic activity (leading to modeling and remodeling). Quite simply, if we challenge our bones on an ongoing basis, they must adapt and grow in order to keep up with the ongoing demand![15] This is why lack of exercise, in adolescence and adulthood, is such a huge risk factor for osteoporosis: no challenge leads to no reward.

However, not all exercise types are equally efficacious for stimulating bone health. Research has found that exercise cannot be static and instead must be dynamic, meaning that the body must be constantly moving.[15] In addition, exercise movements must be different than our "normal" patterns of daily living. The stimulation of bone growth has been found to be most substantial with "relatively abnormal changes produced during unusual loading situations".[15] All of this goes to say that exercises like volleyball and basketball are best for maintaining bone mineral density because of their abnormal movement patterns and high impact. Exercises like cycling and swimming are more ideal for cardiorespiratory exercise as opposed to bone health.

Building lean muscle mass should be a priority for building strong bones, too. Peak rates of bone mineral density are closely timed with peak rates of muscle mass gain, just as losses in one area tend to correlate with losses in the other.[15] High-intensity resistance training involves muscle contractions that pull on the bone surface. This creates another positive stressor and stimulation for growth.[15] All in all, it's important to keep moving and to safely challenge your body within your physical limits. ■

Key Terms

Osteocyte: a mature bone cell
Osteoblast: a cell designed to form new bone
Osteoclast: a cell designed to destroy or eat away bone

What You Need to Know

Having healthy bones is essential in order to have good health. The skeletal system is responsible for providing a site for muscle attachment, protecting the organs, acting as a mineral reservoir and for influencing hormone balance. The skeletal development and breakdown process is affected by several lifestyle and nutritional factors. Bones require vitamins and minerals to remain healthy, and are also significantly affected by sleep, hormones and exercise patterns.

Bone Health Nutrients

Calcium is only one of many different components necessary to help build and maintain strong bones. It accounts for approximately 20% of the entire makeup of bone, while the other 80% is made up of phosphorus, zinc, magnesium, and many other minerals, as well as collagen protein. Several other bone building nutrients that significantly influence bone building and bone health include: magnesium, boron, strontium, vitamin D, vitamin K and Milk Basic Protein. This article presents a snapshot of the most important bone health nutrients and their roles in influencing bone development.

The Many Roles of Calcium

Calcium is a mineral involved in many different functions of the body including muscle contraction, nerve impulse transmission, maintenance of strong bones, immunity and hundreds of others. The adult human body contains approximately 1,200 g of calcium, about 99% of which is present in the skeleton and teeth.[1] The body loses calcium every day, so it is important to get enough calcium in your diet, or to complement it with a high-quality nutritional supplement. It is generally accepted that obtaining sufficient calcium throughout life can significantly decrease the risk of developing osteoporosis. Among other factors, such as regular exercise, gender and race, calcium supplementation during childhood and adolescence appears to be a prerequisite for maintaining adequate bone density later in life. Even elderly osteoporotic patients can benefit significantly from supplementation with dietary calcium. For more information on calcium, see the article titled "Choosing the Right Calcium Supplement".

Magnesium Rich Bones

Magnesium plays a structural role in bone, as approximately 60% of our total magnesium is stored in our bones.[2] A deficiency in this key mineral has been shown to decrease parathyroid hormone (an important hormone involved in calcium regulation), increase inflammation, increase oxidative stress and increase osteoclastic activity.[2] Moreover, supplemental magnesium in osteoporotic women has been shown to increase bone mineral density.[2]

Boron Aids in Absorption

As one of the minerals naturally

occurring in bones, boron is necessary for calcium and magnesium absorption, their adequate reabsorption in the kidneys, and their incorporation into the bone matrix. In a clinical study among post-menopausal women who were not undergoing Hormone Replacement Therapy (HRT), boron was not only shown to significantly diminish urinary losses of calcium and magnesium, but it also raised levels of plasma ionized calcium, beta-estradiol, and testosterone. Boron has been shown to extend the half-life of vitamin D and estrogen, meaning that it helps the body utilize these more efficiently. Supplementation with boron has been found to help retain magnesium and calcium in the kidneys in post-menopausal women.[3]

Strontium's Role in Bone Health

Strontium is an essential nutrient in the development, structure, function and health of the skeletal system. It was the first mineral shown to rebuild bone while simultaneously reducing its resorption. It accomplishes that by making osteoblasts multiply more quickly while slowing down the osteoclasts' activity. Strontium also improves the retention of calcium, phosphorus and protein in the bone, thereby increasing bone strength without lowering their quality.[4] The efficacy of this essential mineral in reducing the risk of fracture in women with osteoporosis has been demonstrated in many clinical trials. Calcium and strontium are both key-players in keeping your bones healthy. These two supplements potentiate each other's action, but they have to be taken separately since they use the same pathways for absorption in the intestinal tract. For more information on strontium, see the article titled "Strontium Citrate: Truly Safe and Effective".

Vitamin D and Bone health

Vitamin D along with vitamin K are the biological signals that direct calcium from the digestive tract where it is absorbed and into the bones.[5] With insufficient (or deficient) levels of these vitamins, calcium is poorly absorbed

and can be inappropriately stored in areas such as blood vessels. The 2 ways the body obtains vitamin D are either through a conversion process in the skin or absorption through the digestive system. However, once produced or absorbed it still must undergo further conversion by the liver and kidneys before it reaches the fully activated form known as calcitrol.[5] We now know that vitamin D has multiple actions throughout the body. When vitamin D levels are deficient (below 80nmol/L or 32ng/mL) then calcium absorption can fall from 30-40% to 10-15%.[6] This means that even though a person is supplementing with the recommended 1000mg/day of calcium, they may only be getting 100mg that is actually absorbed. There is strong evidence that supports the supplementation of vitamin D and calcium together to reduce the risk of fractures.[5,7] Vitamin D levels of at least 80nmol/L have been shown to optimally absorb calcium.[3] This underscores the importance of measuring a person's plasma levels in order to determine what dose is required to reach an optimal vitamin D level. Vitamin D has also been show to improve muscle pain, posture, and balance all of which are key in preventing falls which can lead to fracture.[6,8]

The Different Forms and Functions of Vitamin K

Vitamin K consists of a group of structurally similar, fat-soluble vitamins required for blood coagulation, bone, and liver health and is responsible for a process called carboxylation. This process is essential for activating proteins important for bone mineralization.[9,10] Osteocalcin is the 2nd most abundant protein in bone, after collagen. Its role is to bind calcium in the bone structure or "lattice." [9,10] The other essential role of vitamin K in relation to calcium balance is that it can prevent soft tissue calcification. Vitamin K controls a protein called Matrix GLA.[9] This protein is responsible for protecting soft tissues like blood vessel walls and preventing excess calcium

from being deposited. It acts as a calcium mop in areas of the body that should not be hardened or calcified. The ability of vitamin K to not only increase calcium usage in bone formation but also prevent the calcification of arteries clearly highlights its importance in both bone and cardiovascular health. Vitamin K1 is the more prevalent form in our diet, and is found primarily in leafy green vegetables. Vitamin K2 has several forms, two of which are commonly used as supplements: menatetrenone (MK-4) and menaquinone-7 (MK-7). Over 90% of all studies on bone health have been done with MK-4, but MK-7 has been the subject of more research over the past several years. Vitamin K2 is linked with bone mineral density in the elderly, and correlative studies have noted decreased vitamin K dependent enzyme activity in individuals with kidney stones. MK-4 has been shown in numerous studies to reduce fracture risk, and stop and reverse bone loss. MK-7 has been demonstrated to stimulate osteoblastic bone formation and to inhibit osteoclastic bone resorption.[11,12] In another study, MK-7 caused significant elevations of serum osteocalcin concentration, a biomarker of bone formation.[11,12] Based on the strong historical clinical use and effectiveness of MK-4 and the significance of the new research on MK-7, the best option at this time would be to opt for a supplement containing a high dose of the MK-4 and/or a low dose of the MK-7 forms of Vitamin K2.

Silicon for Skeletal Development

This mineral helps to initiate the mineralization process of bone, and it is no surprise that silicon deficiency is associated with poor skeletal development. (A fun fact for beer lovers: beer contains a relatively high amount of silicon due to the processing of barley and hops).[4]

A Miracle Protein Called Milk Basic Protein

Scientists in Japan have isolated a specific fraction from whey protein called Milk Basic Protein (MBP®), which they have determined to have positive metabolic effects on bone health. MBP has undergone at least six human clinical trials and shows excellent potential to protect bone health and counteract the damaging effects of osteoporosis. The mode of action is thought to be via multiple mechanisms. Simply put, MBP stimulates the activity and proliferation of osteoblasts while simultaneously suppressing the activity and proliferation of osteoclasts. It assists in the absorption and retention of calcium, thereby increasing the preservation of the architecture of the bone matrix including collagen.[13,14,15] MBP does so in a similar, albeit different mechanism than vitamin D. The miracle protein has been shown to increase serum concentrations of osteocalcin, the major non-collagenous protein in bone. Finally, MBP improves the utilization of calcium by virtually "catching" calcium ions, thereby preventing their deposition in other tissues such as arteries and kidneys and maximizing their incorporation into the bones. Bones are composed of dynamic tissues which need a broad range of nutrients to perform their function. Calcium is not the only critical nutrient that is needed for healthy bones. The diet must also contain a wide variety of nutrients including magnesium, boron, vitamin D, vitamin K and, if possible, other complementary proven bone builders such as strontium and milk basic protein. ■

What You Need to Know

Calcium is a crucial mineral, but for optimal bone health, we have to consider a broader approach which encompasses diet, exercise, stress management and supplements such as vitamin D3, silicon, boron, vitamin K2, strontium and Milk Basic Protein. Some of these supplements may seem to have overlapping actions, but they all act in specific and complementary ways. The best supplement protocol is one that combines all of them and that is elaborated according to your own individual needs.

Choosing the Right Calcium Supplement

According to a 2009 Statistics Canada study, 3% of men and 19% of women aged 50 or older reported having been diagnosed with osteoporosis.[1] We now know that several factors are important for bone health such as a healthy diet and lifestyle which includes the avoidance of smoking and excess caffeine, sodium and alcohol. Proper intake of several bone building nutrients, one of which is calcium, is also important. But don't forget, in order for calcium to be efficiently used by the body, many nutrient cofactors are necessary such as vitamin D, vitamin K, magnesium, boron and others.

Ensuring that you are taking the best form of calcium for your body will not only benefit your bones, but will also save you from spending money on a type of calcium supplement that is not going to work well for you or which may provide little value to your body. With so many forms of calcium on the market, choosing one can be complicated indeed. Certain types of calcium supplements may be better for some types of people than others. Some of the most common forms of calcium supplements that are available include: calcium carbonate, oyster shell calcium, calcium gluconate, calcium citrate, calcium citrate-malate, calcium hydroxyapatite, and the more recently discovered calcium lactobionate. Be sure to keep the following factors in mind when choosing a calcium supplement that's right for you.

Give Your Body Calcium It Can Use

Elemental calcium refers to the actual amount of calcium in the supplement. This is what your body can absorb and use for: growing bones and teeth, supporting muscle function, maintaining the heartbeat, nerve impulse transmission, wound healing and blood clotting among other important functions. The Supplement facts panel on a calcium supplement is useful for determining how much calcium a serving actually contains although the bioavailability of the particular calcium type must be taken into consideration. Also pay attention to the serving size when calculating the amount of calcium that is in one serving. For example, a label may or may not provide the total amount of available elemental calcium on a label. See examples of a supplement facts panel in Figure 1. Your body must be able to absorb and use the type of calcium in your supplement in order for it to be of benefit to you. The best way to take your calcium supplement is to divide your daily doses and take 500mg or less at the same time as your meals, when your stomach is actively producing acid to aid digestion.

Choosing the Right Form of Calcium for You

Calcium Carbonate: This is a common form of calcium supplement which is an alkaline-based compound found in rocks, limestone, marine animal shells, pearls, eggshells and snails. This form of calcium provides one of the highest concentrations of elemental calcium (35-40%). For example, a calcium carbonate supplement contains 40 percent elemental calcium; this means that 1,250 milligrams (mg) of calcium carbonate will provide 500 mg of elemental calcium. Yet it has poor bioavailability and requires extra stomach acid production to be absorbed. This type of calcium is found in coral calcium, a form of calcium that has received much attention for exaggerated health claims. There is no research to confirm that coral calcium is in fact a better form of calcium than other forms.

Calcium Citrate: Unlike the alkaline qualities that calcium carbonate offers, calcium citrate has a base that is acidic in terms of pH value. Due to its acidity, it

Who Needs Calcium?

- Calcium deficiency can contribute to bone diseases such as osteoporosis.
- Extreme calcium deficiencies can result in spines that are humped, scoliosis, shoulder roundedness and reduced height.
- Prescription drugs such as antidepressants and birth control, are well known for lowering calcium levels.
- Soda-drinkers lose large amounts of calcium drinking soda according to a 2001 study from Creighton University.
- A report from Tufts University in Boston found that soda pop presented problems of calcium-leaching. A sampling of 1,413 women found that regular soda drinkers had significantly lower bone densities than women who only had a soda once a month.
- Pregnant women require additional calcium.
- A study from the Journal of the American Medical Association noted that raising calcium intake during pregnancy can assist in stabilizing blood pressure and supports a baby's calcium needs.
- Women lose bone density after age 35 and both women and men both have a higher risk for calcium deficiency after age 50.
- Postmenopausal women lose approximately 3%-5% of their bone mass per year.
- Chemotherapy has a negative impact on many of the minerals in the body, especially calcium levels.
- Exposure to toxic metals and radiation increases calcium demands.

requires less natural stomach acids to be produced in order for it to be absorbed. This type of calcium is absorbed to a greater extent than calcium carbonate.[2] An analysis of 15 randomized trials concluded that calcium citrate was absorbed 22% to 27% better than calcium carbonate, whether taken on an empty stomach or with food.[5]

Oyster Shell Calcium: Although it may seem to be a natural form of calcium, and therefore higher in absorbable calcium, the calcium in the oyster shell as well as bone meal and dolomite, are more susceptible to have toxic levels of lead due to difficulty in maintaining quality control. It is better to avoid these natural forms of calcium.

Calcium Gluconate, Lactate and Phosphate: All three of these forms of calcium offer lower elemental calcium concentrations or bioavailability. It would be necessary to take large amounts of calcium gluconate to obtain calcium requirements as it is only 13% elemental calcium, and it is not certain how bioavailable this form of calcium really is.[3] Calcium lactate is present in foods such as aged cheese and baking powder. It is common for this form of calcium to be used as an antacid and is added to fruits to maintain their firmness and to extend their shelf life. The bioavailability of this form of calcium is acceptable because it can be absorbed at various pH's in the body; however, it has a relatively low amount of elemental calcium available, 9%.[3] Calcium phosphate also has an absorption level similar to that of calcium carbonate and has an elemental calcium amount of 31%.[3]

Calcium Lactobionate: This form of calcium is also referred to as lactobionic acid and it is not considered to be a useful source of calcium as much as it is known for its unique ability to help the body absorb more calcium from the diet and from supplements, therefore preventing calcium from accumulating in the arteries. It does this by binding to calcium ions from the diet that are in the stomach, intestines and the blood and helping to take them to the site where they are needed most, in the bone.[4] The solubility of this form of calcium is sixty-five times higher than other forms of calcium like the citrate which is considered one of the most bioavailable forms. Originally found in the yogurt from Bulgaria and regions nearby, the Japanese were able to identify this unique form of calcium and its ability to help absorb additional calcium and increase bone mineral density. In addition, lactobionic acid also increases the production of equol by the gut microbes. Equol is a unique isoflavone similar to the soy isoflavanoid daidzein but more powerful in its bone health effects. Lactobionic acid is unique in that it helps the body to absorb more calcium from the diet and therefore helps to maintain optimal bone health without

necessarily increasing intake of calcium above 1000mg per day.

Calcium Citrate-Malate: Calcium citrate-malate is formed from the calcium salt of citric acid and malic acid consisting of variable composition. It's particularly valuable since it has been demonstrated to be highly bioavailable. Calcium citrate-malate's bioavailability is possible due to its water-solubility and its method of dissolution. Upon being dissolved, it releases calcium ions and a calcium-citrate complex. Calcium ions are directly absorbed into intestinal cells. Although calcium citrate-malate contains only about 26% elemental calcium, it is one of the most well absorbed forms of calcium. The special structure of calcium citrate-malate makes it 6 to 9 times more easily dissolved in the stomach than plain calcium citrate, with an absorption rate of 36-37% in tablets and capsules, or higher if dissolved in orange juice.

If you are a vegetarian and looking for a highly bioavailable calcium supplement, this is the form you will want to consider taking. AOR offers calcium citrate-malate in several supplements including: Ortho•Bone Vegan, Multi Basics 3, Essential Mix, Ortho•Core and Ortho•Minerals. Calcium citrate-malate is well-absorbed even when taken alone, and is recommended for individuals who have low levels of stomach acid, for those who are older, who are taking stomach acid blockers, or who have absorption or inflammatory bowel disorders.

Calcium Hydroxyapatite and Microcrystalline Hydroxyapatite Complex: Although many foods provide various calcium salts, human and animal bones are the only natural source of calcium hydroxyapatite. Be aware that there is a synthetic form of calcium hydroxyapatite called calcium orthophosphate; this is not the same as microcrystalline hydroxyapatite complex known as MCHC. MCHC is the most efficacious calcium hydroxyapatite when processed at low temperatures, and it is derived from natural sources. It is derived from the raw bones of free-range cattle from New Zealand where the cows are raised with no exposure to antibiotics, pesticides, hormones or other toxic chemicals. To preserve its full spectrum of nutrients and minerals, the bone extract needs to be processed at very low temperatures. This kind of calcium is significantly bioavailable to the body compared to other forms of calcium and as a result is easier to absorb. MCHC has been shown to stop and reverse bone loss in controlled human clinical trials.[6] The benefits of MCHC are due to not only its calcium content, but also the growth factors, peptides, mucopolysaccharides and other micro nutrients that work together to target bone maintaining and building processes. One study demonstrated that ossein-hydroxyapatite compound is an effective and safe agent for the prevention of bone loss in postmenopausal osteopenic women. After they took the ossein-hydroxyapatite compound, there were significant increases in BMD observed in this group of patients.[7] Therefore, MCHC is not just a calcium source but a quality bone building nutrient in itself. However, it is not suitable for vegetarians or vegans as it is sourced from animal bones.

The body requires several nutrients and micro nutrients in order for calcium to be effectively used in the body; the calcium it receives must also be in a usable form. According to research, calcium citrate-malate has demonstrated impressive results for bone maintenance and is suitable for vegetarians. However, MCHC has proven to be the best all-around bone protection ingredient as it offers more than calcium to the bones. Its abilities to stimulate bone growth and prevent bone resorption makes it a superior bone building complex. Although other forms of calcium supplements may also offer some moderately beneficial results, it is important to get the best bone protective ingredients to ensure that your body has the nutrients it needs to stay healthy. ■

Figure 1.

Examples of Label Formats Displaying the Amount of Calcium in a Supplement	
The following label does not specify the exact amount of Calcium from the source compound. Since calcium citrate-malate is about 26% calcium, we have to assume that there is only about 130mg of calcium in one capsule.	
Supplement Facts:	
Serving Size:	**1 capsule**
Calcium citrate-malate	**500mg**
The following label provides the exact amount of Calcium from the calcium citrate-malate compound. Since calcium citrate-malate is 26% calcium, we can assume that there is about 1923mg of the whole compound per capsule yielding 500mg of elemental calcium.	
Supplement Facts:	
Serving Size:	**1 capsule**
Calcium (citrate-malate)	**500mg**

What You Need to Know

Calcium comes in a variety of forms, but it is important to realize that not all calcium supplements are created equal. Choosing a form of calcium that will work well for you will depend on your digestive system and what your calcium needs are. According to research, one of the most well absorbed vegetarian forms of calcium is calcium citrate-malate. Microcrystalline hydroxyapatite complex (MCHC) is known as the most beneficial form of calcium since it offers more than just calcium; it provides several bone enhancing factors including growth factors, peptides, mucopolysaccharides and other micronutrients.

Nitric Oxide and Bone Cell Formation

Nitric Oxide (NO) is a simple molecule consisting of one atom of nitrogen and one of oxygen, making it even simpler than water. Research into the effects of this small but important molecule began in the 1970's when scientists started to examine why blood vessels relaxed when certain compounds were added. This led to the discovery of NO and its amazing effects in the body, with NO being named the molecule of the year in 1992. In 1998, twenty-some years after this research first began, a Nobel Prize was awarded to these researchers for their breakthrough discoveries regarding NO. Over the last two decades NO research has continued to grow, and there has been an exponential increase in the number of publications on this fascinating molecule. Some health promoting effects of nitric oxide include increased circulation, lowered blood pressure, enhanced digestion, enhanced libido, improved immune system and stronger bones.

How NO is Produced in the Body

The conventional method of NO synthesis is from the amino acid L-Arginine (see Figure 1). L-Arginine is oxidized via a series of steps involving a family of enzymes called nitric oxide synthases (NOS). There are essentially three common NOS termed isozymes; these are iNOS, eNOS and nNOS. Each of these enzymes plays a different role in the generation of NO in different tissues like the nerves, endothelium or blood vessels or on demand. In each case however, normal oxygen conditions (also called "normoxia") as well as a neutral to high (alkaline) pH level are required. When these conditions are met the NOS-dependent conversion of L-Arginine occurs efficiently. Production of NO is the primary reason for the dietary intake of L-Arginine. However, under low oxygen conditions (also called "hypoxia") the conversion of L-Arginine to NO is severely limited. Low oxygen conditions can occur for a variety of reasons. For example, partial or complete blockage of a blood vessel (ischemia), conditions of extreme physical exercise or high altitudes can all result in reduced blood flow and thus reduced oxygen delivery to the body's tissues and cells. Moreover, such low oxygen conditions

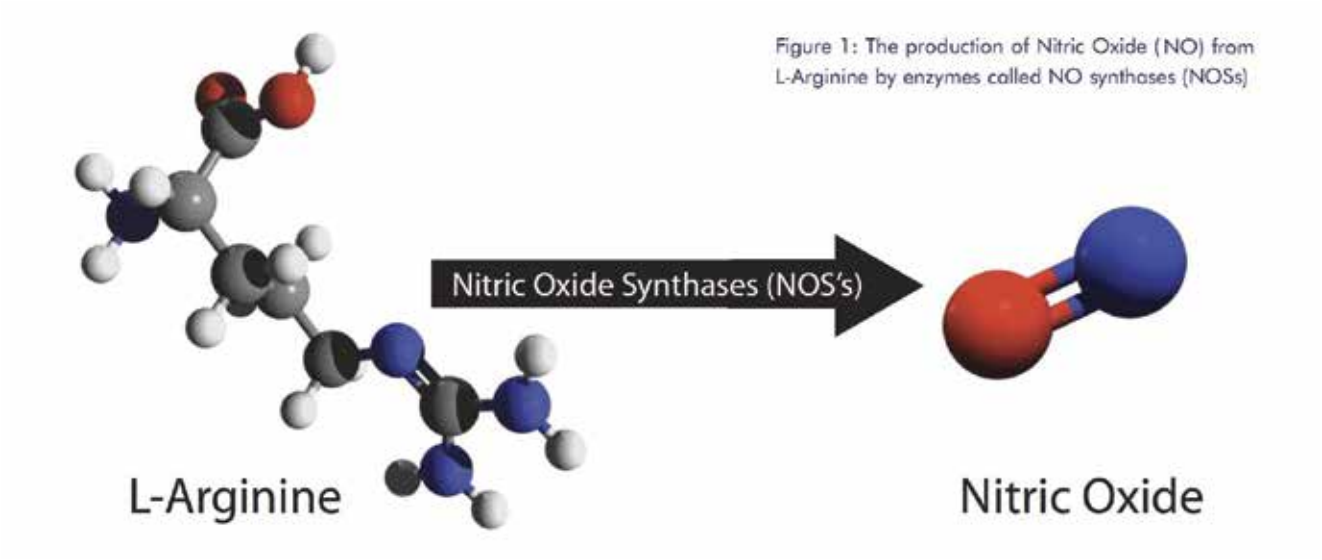


Figure 1: The production of Nitric Oxide (NO) from L-Arginine by enzymes called NO synthases (NOSs)

are also accompanied by an increased production of lactic acid which reduces pH making the tissue condition both hypoxic and acidic.

Another Way to Produce Nitric Oxide

A novel pathway to NO generation from dietary nitrates has been discovered by researchers at the Karolinska Institute in Stockholm, Sweden and by researchers from the University of London, England. The Swedish and English researchers were trying to discover why certain diets, like the Mediterranean diet, vegetarian diets, Japanese diets and the famed DASH diet (Dietary Approaches to Stop Hypertension) were particularly protective of the heart. Both groups independently reported that the key to the success of these diets was the consumption of leafy green vegetables, and that a key component of all these diets was the high nitrate content. The researchers proposed that the nitrate was converted into NO via a reductive process as follows: essentially, the nitrate is reduced in the mouth by bacteria that are normally present on the back of the tongue. These specialized bacteria use the nitrate to help them make energy in the form of ATP. In return, the bacteria utilize their own nitrate reducing enzyme called Nitrate Reductase to generate nitrite. This special relationship is an interesting example of human-bacteria symbiosis: a mutually beneficial relationship. The nitrite is a much more active molecule than nitrate and is present in high concentrations in the saliva which is swallowed into the stomach where conditions of low oxygen (relative to the mouth) and high acid are present. These conditions are ideal for further reduction of nitrite into NO. The entire reduction process of nitrate into nitrite and then into NO occurs without the intervention of NOS enzymes. These enzymes wouldn't be active in these low oxygen and low pH conditions anyway. It should be noted that low oxygen and low pH conditions don't just occur in the stomach, they can also occur throughout the body in certain situations including extreme physical exercise, heart disease and psychological and physical stress. Both pathways of NO generation are depicted in Figure 2.

How Bone Remodeling Occurs

Bone is a complex tissue composed of several cell types which is continuously undergoing a process of renewal and repair termed 'bone remodeling' (see Figure 3). The two major cell types responsible for bone remodeling are osteoclasts ("bone eaters"), which breakdown bone, and osteoblasts ("bone builders"), which form new bone. During the bone remodeling cycle,

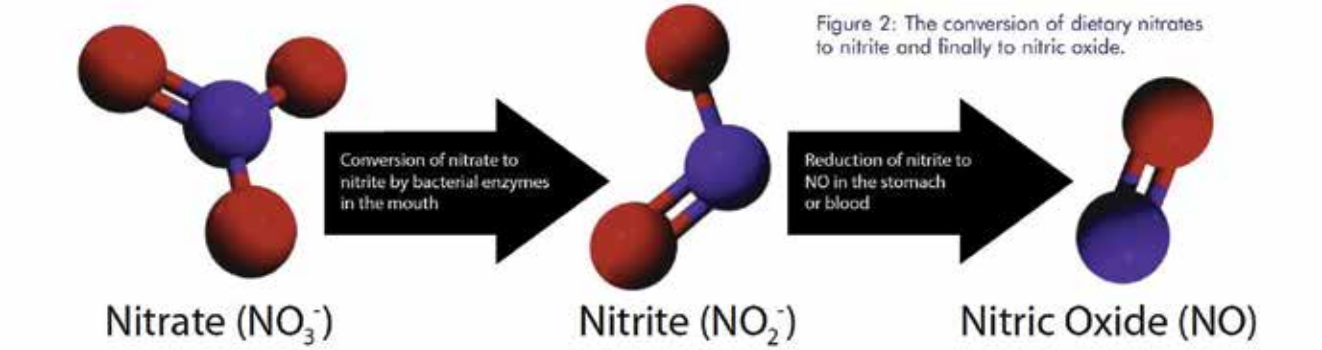
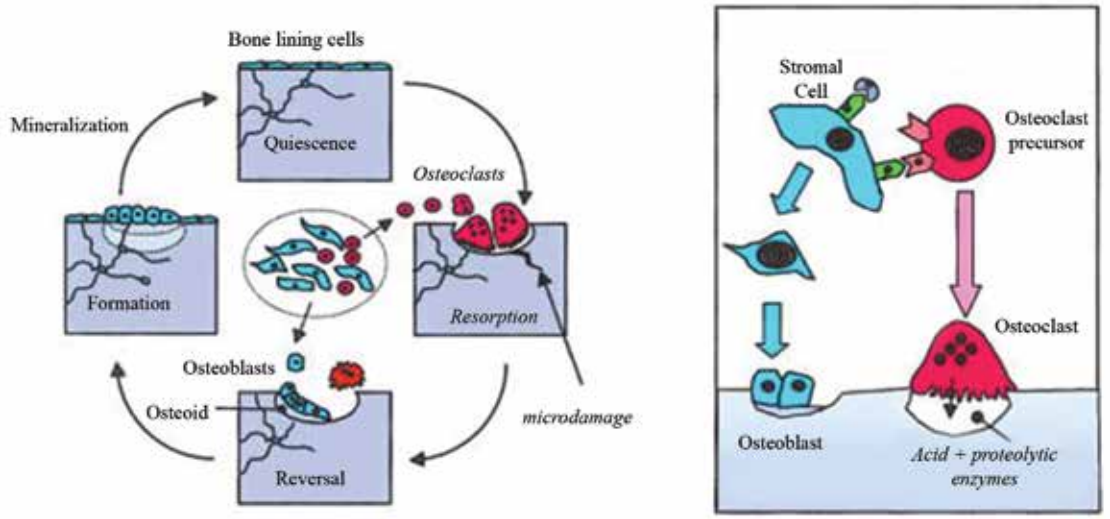


Figure 2: The conversion of dietary nitrates to nitrite and finally to nitric oxide.

Figure 3. The bone remodeling cycle



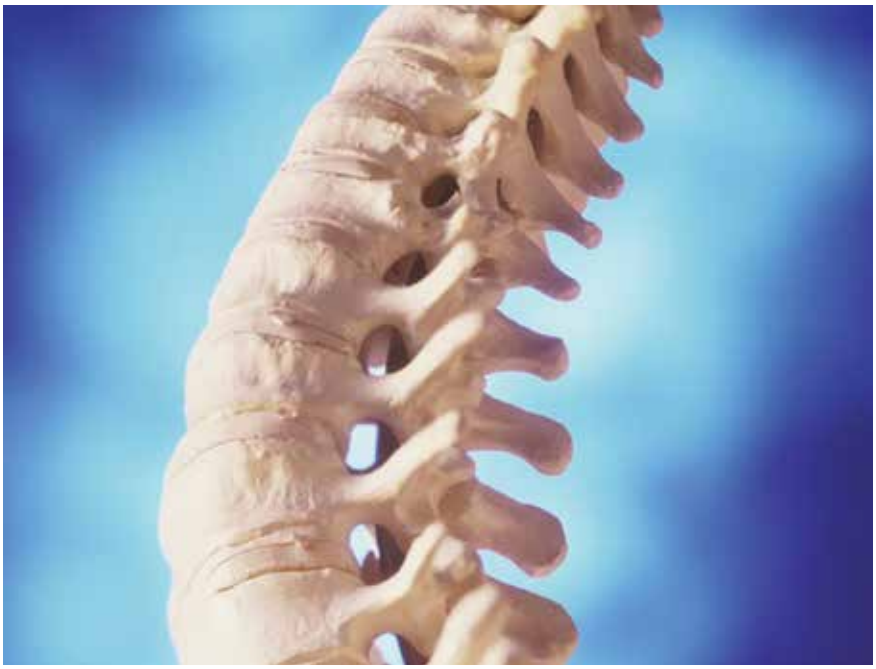
old or damaged bone is removed by osteoclasts, which secrete acid and enzymes that digest the bone onto the bone surface. Subsequently the osteoclasts migrate away from the area of bone undergoing resorption and die. They are replaced by osteoblasts, which lay down new bone matrix in the form of osteoid. Later, the osteoid becomes calcified to form mature bone. During bone formation, some osteoblasts become embedded within the bone matrix, and become osteocytes, a third cell type unique to bone. Osteocytes interconnect with one another and with cells on the bone surface via channels in the bone matrix. It is thought that osteocytes act as sensors of mechanical stress in the skeleton, by detecting and responding to changes in fluid flow which run through cannaliculi in the bone.[3-5] Bone remodeling is regulated by several systemic hormones, such as parathyroid hormone (PTH), vitamin D, sex hormones (e.g. estrogen) and calcitonin, as well as by local factors including NO, prostaglandins, growth factors and cytokines.[6]

How is Nitric Oxide (NO) Involved in Bone Health?

Nitric oxide appears to have a two-fold effect on osteoblast activity. Studies *in vitro* have indicated that the small amounts of NO which are produced by osteoblasts may stimulate their own growth as well as the production of immune modulating proteins.[7] Whilst some investigators have shown that slow release NO donors stimulate osteoblast growth and differentiation *in vitro,*[8-10] other workers reported that NO donors and NOS (Nitric Oxide Synthase) inhibitors had little effect on osteoblast growth or differentiation, except at high concentrations where osteoblast growth actually seemed inhibited.[11,12] The most compelling evidence supporting a role for NO in osteoblast function comes from studies of eNOS (endothelial NOS) in animals. Two groups of investigators have reported major defects in bone formation and osteoblast activity and a reduced growth response to administered estrogen both *in vivo* and *in vitro* in eNOS deficient animals. The molecular mechanisms responsible for this remain to be defined, but indicate the existence of an important interaction between eNOS and the molecular pathways involved in osteoblast differentiation and function.[13,14] In addition, a possible mechanism for the inhibition of osteoclast activity by NO is the modification of cathepsin K (a bone regulating enzyme). Cathepsin K is highly expressed in osteoclasts and plays a key role in the bone resorption mechanism, since it degrades bone collagen. NO and several NO donors have been shown to inhibit the activity of this enzyme.[15]

What You Need to Know

Bone health is a key component to healthy aging. As the majority of our population is now entering or into its senior years, it is imperative that we look at our options, both novel and conventional, when it comes to keeping our bones strong. This article has focused on the novel yet effective nitric oxide molecule and its role in keeping the bone remodeling process robust over time. Our bones are very much alive and it is vital that our system keeps removing the old bone and laying down new bone in its place. Consuming foods rich in nitric oxide producing nitrate in combination with other key bone building nutrients (such as calcium, magnesium, vitamins D, C and K) is a potent recipe for maintaining bone integrity and worth considering for preventing or managing concerns related to poor bone health.



Strontium Citrate Demonstrates its Safety and Effectiveness

Introduction to Strontium

In 2002, AOR introduced the world's first strontium citrate as a dietary supplement for bone health. There have been some recent concerns about strontium's safety as well as a lack of information regarding strontium citrate. The goal of this article is to discuss the foundations of such concerns and to increase awareness about new research on the safety and effectiveness of strontium citrate.

Strontium is a natural element. In nature, it is found in highest amounts in the ocean and consequently in certain bony fish. 99% of the strontium found in the human body is in the bone. Because strontium and calcium have very similar molecular structures, the body treats them much the same.

Although much of the clinical research on strontium has been done recently on a compound called strontium ranelate, which is a patented pharmaceutical drug used in Europe (but not in Canada or the USA), it boasts a rich history of use prior to being known as strontium ranelate. Strontium was discovered in ore in the late 1700s and isolated in the early 1800s, but its medicinal effects were first identified in the late 1800s. Strontium was introduced into various medical pharmacopoeias around the world after first appearing in Squire's Companion to the British Pharmacopoeia in 1884.[1]

Which Form of Strontium?

Since then, strontium has been combined with various compounds to form strontium salts such as strontium salicylate, strontium cinnamate, strontium chloride, strontium lactate and strontium gluconate, all of which have been used for medical purposes. Ranelic acid is a synthetic compound not found in nature and is the most recently studied partner for strontium. However, it is the elemental strontium that is important. Early studies demonstrated this fact by basing their doses, evaluations and conclusions on the amount of elemental strontium given and not those of the entire compound.[1]

In these early studies, up to 1750 mg/day of the strontium ion from strontium gluconate and strontium lactate were found to be safely tolerated in patients with bone cancer or postmenopausal osteoporosis receiving strontium from 3 months to 3 years. In bone cancer patients, remineralization was seen in areas where bone had become weak, and patients reported less pain and feeling better overall.[1]

Strontium Citrate

Although strontium citrate has not been well studied, we can imagine that the strontium from ranelate is absorbed into the bone at a similar rate as strontium from citrate. A recent study in rats administered either strontium ranelate or strontium citrate providing the same amounts of elemental strontium per day. They found that the amount of strontium accumulated in the bone from either source was the same.[2] At last, at least two studies have been completed in humans using strontium citrate.[3,4] However, the strontium was given in combination with other nutrients known to benefit bone health.

The First Study

In the first study, subjects were given an algae-derived mineral supplement providing calcium, magnesium and trace minerals (including strontium) along with additional nutrients known to benefit bone health such as additional strontium citrate, vitamin D3, boron, vitamin C and vitamin K2 as either MK-4 or MK-7.[3] A third group did not receive extra strontium, vitamin K, vitamin C or activity and lifestyle advice like the first two groups. While all three groups experienced increases in bone density (even the group that did not receive extra strontium), the group that received strontium at 680 mg per day and 1.5 mg of MK-4 performed better than the group receiving more vitamins and minerals but only 100 mcg of MK-7.

The Second Study

The second study out of Edmonton, Alberta administered the same amount of strontium from citrate, vitamin K2 in the form of MK-7, 2000 IU of vitamin D3, 25 mg of magnesium, and 250 mg of DHA omega-3 fatty acids from

Conclusions We Can Draw from the New Strontium Citrate Studies

1. **There is now human evidence on strontium citrate**. These are the first studies to examine strontium from citrate in humans, although many other forms have been studied.
2. **Strontium from citrate is safe to take at 680 mg of elemental strontium per day for at least 1 year** (although we have already seen that elemental strontium is safe at doses approaching 2 g per day for up to 3 years, and we will later see that strontium ranelate is safe and effective for up to 10 years!).
3. **Take strontium with other proven bone health nutrients.** The fact that the strontium citrate was evaluated combined with a whole bone health treatment regimen rather than on its own is actually a good thing, since it is a more realistic and prudent approach than taking strontium alone. Strontium is not a replacement for calcium or any other bone health nutrient; rather it is an addition that can help build bone.
4. **Strontium is an important trace mineral, a deficiency in which may actually contribute to osteoporosis.**[4] The fact that the third group in the first study that didn't receive extra strontium yet also saw some bone density improvements can be explained by the following: the algae-based supplement also contained strontium amongst the trace minerals naturally present, which is a testament to its importance in the human diet and to the likelihood that its presence contributed to the small but positive results gained by the third group.
5. **Take it regularly!** The second study shows how important compliance is in order to achieve good results.
6. **Comparing strontium citrate vs. ranelate.** The second study is the first to compare, though indirectly, the results in humans from strontium citrate versus strontium ranelate!

fish oils.[4] The subjects were advised to get their calcium from foods rich in calcium rather than take a calcium supplement. They were also advised to engage in impact physical activity. Over the course of one year, bone mineral density increased the most at the spine and at certain points in the hip. The most exciting thing is that the increases in bone mineral density were twice as good as the results that some of the subjects had previously seen with bisphosphonate treatment for one year, and at least equal to and even greater in some cases than strontium ranelate treatment for one year! Equally important, the subjects who did not take the supplements every day for the whole year were evaluated separately, and no significant differences were found in their bone density scores after the study.

What About the Adverse Effects of Strontium?

Strontium ranelate has been associated with, but not necessarily the cause of, rare cases of gastrointestinal disturbances, minor skin rashes, blood clots and memory loss, in descending order.[5] Two other studies pooled information obtained from physicians working with patients in their practices and found that people who had osteoporosis appeared to have a higher risk of blood clots regardless of whether or not they had been treated with strontium ranelate, bisphosphonates or other post-menopausal osteoporosis treatment.[6,7] For strontium ranelate, the blood clot effects were measured within the first year of use.[7] In the two recent studies using strontium citrate for 1 year, there were no adverse effects of any kind either self-reported or from blood samples.[3,4]

Strontium and Bone Fragility Rumours

There has been some concern in the past few years that strontium may eventually increase the risk of fractures by reducing tensile strength of the bone (the ability of bone to resist pulling forces). All of this concern has been caused by a single article that claimed that strontium accumulates more so in the thicker outer portion of the bone (cortical bone) rather than the inner matrix, or cancellous bone, that is most affected by osteoporosis. In theory, this would increase the risk for breakage. However, a brief overview of several studies will show us that this theory has been disproven. In fact, the opposite has been shown to be true, with several long-term human studies showing good safety and effectiveness.

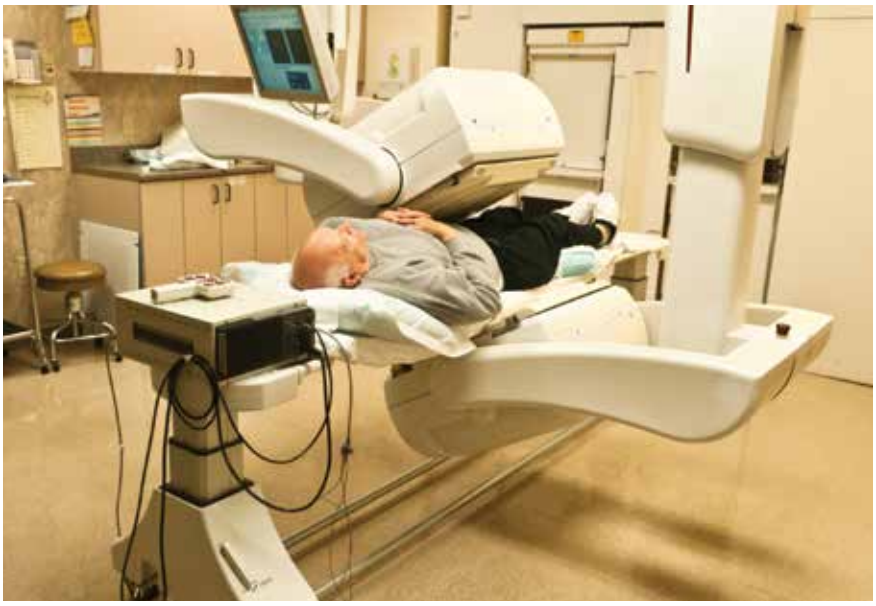
Let's start logically by saying that of the various forces on bone that cause fractures, tension forces are the least common culprits.

A review of strontium's effects on bone architectural structure found

that overall, strontium works.[8] Several studies found that blood indicators of bone formation increased by about 8% while markers of bone deterioration decreased by about 12%, and that these markers were sustained from 3 months to 3 years with strontium ranelate use.[8] One of these studies took bone samples after treating subjects with strontium ranelate for up to 5 years. The bone samples showed a 14% increase in trabeculae number, a 16% decrease in trabecular separation (these are measures of the quality of the cancellous bone) and an 18% increase in cortical thickness.[9] This shows that strontium positively affects both the inner and outer bone structure. These same studies also found that for every 1% increase in bone density of the femoral neck (the thin part of the thigh bone which insets into the hip socket), there was a 3% reduced risk of a fracture of the spine.[8] These results counter the argument that bone mineral density scans show inflated readings only because strontium is a denser mineral than calcium. While this is true, increases in bone mineral density as measured by scans do indeed equal a reduced incidence of fractures and improvements in bone formation markers.

Several more recent studies have found that strontium is only present in bone formed during strontium treatment, that bone formation is actually higher in cancellous bone than cortical bone during the 3 years of treatment with strontium, and that even with the replacement of up to 4.5% of calcium ions by strontium, bone mineral quality is maintained even up to 3 years of treatment with strontium.[10,11,12] An extension of these trials found that 5 years of treatment with strontium ranelate with calcium and vitamin D in women over 80 years increased quality of life, number of years, and was actually cost saving due to reducing the risk of fracture.[13]

The longest study to date examined the effect of strontium ranelate when used continuously for 10 years.[14] This is a very long time for a substance used as a supplement to be studied! Amazingly, they found that bone mineral density continued to increase every year over the 10 years and that the incidence of fracture was maintained at the end of the study compared to the earlier years of the study and lower compared to a placebo group. No bisphosphonate has had the same long-term measure of success.[15] Best of all, there were relatively few adverse side effects from the treatment.



So while the reduced tensile strength argument seems possible in theory, clinical human studies have clearly shown otherwise!

Strontium as a Treatment for the Treatment

Bisphosphonates are a group of osteoporosis drugs known to work well for the short term but can have devastating opposite effects after several years of use. In this case, bone fragility increasing as a result of the treatment is proven to be true in numerous clinical studies. Several studies have suggested that strontium ranelate is a possible solution for those who have experienced excessive bone deterioration after taking bisphosphonates.[16,17] They found that subjects who had been treated with bisphosphonates actually had a delayed response to strontium ranelate for the first 6 months, where not many changes in the bone were seen. Between 6-12 months, the bone growth occurred at a similar rate to those who had never taken bisphosphonates. Strontium may therefore help restore bone health for victims of failed bisphosphonate treatment, albeit a slower recovery.

Research on Strontium Continues and Expands

Strontium's mechanisms of action are beginning to be understood. It is thought that strontium activates calcium-sensing receptors and also influences the expression of genes that control bone formation and bone breakdown.[8] One study has also caught a glimpse of how strontium is lost from the bone after stopping treatment with strontium ranelate.[18] Bone strontium content declined by about 27% after 3 months of stopping use and by about 33% after 6 months of stopping use. This is a small amount considering they found that bone strontium content is about 1% on average after 3-8 years of use. Bone strontium loss is suggested to be less marked over time, and strontium may remain in bone for years after treatment. According to this study, the longer strontium is taken, the longer it takes for the bone to lose strontium after stopping treatment.

Some of the newest research has shown that strontium benefits men with osteoporosis the same as it does

What You Need to Know

Strontium is strontium, and it is treated the same way by the body no matter what salt form it is in. Several human studies on strontium citrate have emerged, producing the same positive results as other forms of strontium in combination with other important bone health nutrients and a healthy lifestyle. However, inconsistently or sporadically taking strontium may not produce positive results. Strontium citrate has not produced the same adverse effects as strontium ranelate during the first year of use. The claim that strontium negatively impacts the quality of bone structure and integrity is unfounded and false; in fact, it has an overwhelmingly positive effect on the quality of bone mineral, it increases bone density and bone formation, and it reduces the risk of bone fractures. Improvements in bone density scans really do correlate with increases in bone formation and reduced fractures. Strontium has indeed been safely and effectively used with relatively few adverse effects for periods of up to 10 years! We have even seen that strontium is a potential treatment for failed conventional treatment with bisphosphonates, as well as for other types of people and health concerns. Finally, Health Canada has granted AOR's Strontium Support II containing strontium citrate an NPN based on the evidence presented here, approving of its safety and effectiveness. For more details on strontium, please see AOR's previous Advances magazines Volume 2 Issue 3 and Volume 3 Issue 4.

women.[19] Strontium has also been shown to be a potential treatment for knee osteoarthritis, providing some structural support, reducing pain symptoms and improving physical function of the knee joint in osteoarthritis patients.[20] The use of strontium in bone and heart implants may even be on the horizon since new research shows that it is degraded slower than other materials like magnesium typically used in implants.[21]

The Final Word

Since its discovery until today, strontium's popularity has risen and fallen on waves of uncertainty of whether it is safe, whether it is effective, what it is effective for, how it works, and how long it works for, and other unclearly answered questions. But today, in spite of unfounded arguments, the evidence points to the overwhelming safety and effectiveness of strontium for healthy bones. ■

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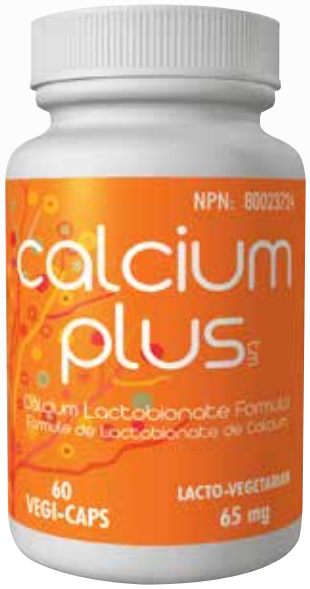
AOR Bone Supplement Comparison Chart

Product	Recommended For	Advantages	Contraindications	Dosing
	Osteoporosis Osteopenia Post-menopause	Powerful bone health formula Most bioavailable calcium source Stimulates bone growth Now with MK-4 & MK-7	Impaired kidney function Warfarin	10 caps/day Max. of 5 caps at once
	Osteoporosis Osteopenia Frail or small women of all ages	Combines Ortho Bone with Advanced Bone Protection Most advanced & complete bone formula Helps increase bone density Stimulates bone growth Supports collagen	Impaired kidney function Warfarin Severe milk allergies	10 caps/day Max. of 5 caps at once
	Vegans & vegetarians Maintenance Prevention Family history	Most advanced vegan bone formula Most bioavailable vegan calcium source Now with MK-4 & MK-7	Impaired kidney function Warfarin	10 caps/day Max. of 5 caps at once
	Maintenance Prevention Family history	Most bioavailable calcium source Stimulates bone growth Now with MK-4 & MK-7, vegetarian glucosamine	Impaired kidney function Warfarin	6 caps/day Max. of 3 caps at once
	Use with Ortho Bone or Bone Basics	Helps build stronger bones Denser mineral than calcium	Impaired kidney function	2 capsules best taken together Take 2 hours away from calcium and food
	Use with Ortho Bone, Bone Basics, or other calcium regime	Stimulates bone growth Inhibits bone break down Supports collagen One small capsule daily OK for milk intolerance	Severe milk allergies	1 cap/day
	Use with Ortho Bone, Bone Basics, or other calcium regime	Stimulates bone growth Increases bone density Inhibits bone break down Supports collagen OK for milk intolerance	Impaired kidney function Severe milk allergies	2 capsules best taken together Take 2 hours away from calcium and food
	Use with calcium and vitamin D	MK-4 & MK-7 Enhances calcium absorption Directs calcium from arteries into bones	Warfarin	1 cap/day
	Children & adults Use with calcium and vitamin k	Enhances calcium absorption Capsule: 1 capsule daily Liquid: Calibrated dropper, Children's formula available		1 cap/day OR 0.2 mL/day
	Use with Ortho Bone or Bone Basics or other calcium regime	1 capsule daily Prevents calcium excretion Backup in magnesium deficiency Enhances vitamin D		1 cap/day

calcium plus



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