Science-based, Targeted Nutritional Support for Optimal Fracture Healing
Each year, an average of 6 million people in the United States will break a bone, accounting for 16 percent of all musculoskeletal injuries and more than 3.5 million emergency department visits. In fact, the average citizen in a developed country can expect to sustain two fractures over the course of his or her lifetime. Prior to age 75, the most common site of fracture is the wrist. In those over age 75, hip fractures represent the most common broken bone. By 2025, age—or osteoporosis—related fractures are projected to increase to more than 3 million per year, solely on the basis of growth in the elderly population at risk.

In response to a bone fracture, the body acts swiftly to initiate healing, as cells in the neighboring tissue send out chemical messengers that encourage the growth of small blood vessels and, eventually, differentiation of mesenchymal stem cells into cartilage, bone, and fibrous tissue. While most broken bones heal without incident over time, approximately five to 10 percent of bone fractures fail to heal normally, resulting in delayed healing or non-union.

The nutritional stage set for healing can influence the speed, comfort and completeness of the bone renewal process. Substantial clinical research supports the role of nutritional supplementation—including protein, natural antioxidants and anti-inflammatories, minerals, and vitamins—in bolstering and accelerating fracture healing. However, fracture healing is a complex biological process that requires multi-nutrient support and it may be difficult for patients and their physicians to find a high-quality, pharmaceutical-grade supplement that addresses the specific nutritional needs of fracture patients.

**Physiology of Fracture Healing**

During the last two decades, our understanding of fracture healing has evolved rapidly. Bone is one of the few body tissues that can heal without forming a fibrous scar and, as such, the process of fracture healing recapitulates bone development and may be considered a form of tissue regeneration. The complex cell and tissue proliferation and differentiation processes involved in fracture healing are regulated by growth factors, inflammatory cytokines, antioxidants, hormones, amino acids, and other nutrients.

The process of fracture healing can be divided into three phases:

- **Inflammatory phase**—This first stage of healing begins immediately upon fracture, when a hematoma forms, setting off a cytokine cascade that leads to the influx of macrophages and inflammatory leukocytes into the fracture gap.

These cells scavenge debris and begin producing the pro-inflammatory agents that initiate healing. Inflammation triggers growth of new blood vessels, as well as differentiation of cells into bone-building osteoblasts and cartilage-forming chondroblasts. Over the next few months, these cells form new bone matrix and cartilage, while osteoclasts break down and recycle bone debris.

- Reparative phase—The second stage of healing begins approximately two weeks after the fracture occurred. During this time, proteoglycans and collagen produced by the osteoblasts and chondroblasts begin to consolidate into a soft callus, which is eventually resorbed and replaced by a hard callus through endochondral ossification and direct bone formation over a six- to 12-week time period.

- Remodeling phase—Although the hard callus is a rigid structure that provides stability, it does not fully restore the biomechanical properties of normal bone. In the final stage of fracture repair, the hard callus matures and remodels into strong, highly-organized lamellar bone with a central medullary cavity, a process orchestrated by osteoblasts and osteoclasts.

**Figure 1. Stages of Fracture Healing**

![Figure 1. Stages of Fracture Healing](source: McGraw Hill)

**Nutritional Demands of Fracture Healing**

Each stage of the fracture healing process is accompanied by increased nutritional demands. The trauma of the fracture itself causes oxidative stress, releasing free radicals that may tax or even overwhelm the body's antioxidant reserves. The fracture healing process also requires significant energy, an adequate blood supply and an ample store of amino acids for new protein synthesis.

**Using Nutrition to Support Fracture Healing**

*Meeting Energy Demand*

While a normally active adult requires approximately 2,500 calories a day, a patient with multiple fractures may need up to 6,000 calories per day to meet the energy requirements for healing.\(^2\) If this demand is not met, the fracture healing process may be compromised.\(^3\) Increasing caloric intake to meet increased metabolic demand may help to promote healing.

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**Assuring Adequate Protein**

Protein comprises approximately half of bone by volume. When a fracture occurs, amino acid building blocks are needed to synthesize a new structural bone protein matrix. Amino acids of specific importance for fracture healing include lysine, arginine, proline, glycine, cysteine, and glutamine. For example, lysine is known to enhance calcium absorption, increase the amount of calcium absorbed into the bone matrix, and aid in tissue regeneration. In addition, protein supplementation increases growth factors such as insulin-like growth factor-1 (IGF-1), a polypeptide that exerts a positive effect on skeletal integrity, muscle strength, immune response, and bone renewal.\(^1,2\)

Protein deficiency leads to a rubbery, rather than rigid, callus. Multiple studies have demonstrated acceleration of fracture healing with even a modest 10- to 20-gram increase in protein intake. Supplemental protein is particularly important in those with low baseline protein intake or protein malnutrition. In fact, among elderly patients with hip fracture, poor protein status at the time of fracture is predictive of fracture outcome. Patients with poor protein status take longer to heal and are more likely to suffer complications, including death.\(^3,4,5\)

**Increasing Antioxidants and Anti-Inflammatories**

When a fracture occurs, free radicals are generated by the damaged tissues, particularly as tightly-bound strands of collagen in the mineral phase of bone are snapped. These ruptured collagen strands interact with oxygen, giving rise to free radical metabolites, which are associated with inflammation, further collagen breakdown and excessive bone turnover.\(^6\) In patients who have sustained bone fracture, increased free radical production may overwhelm the body’s natural antioxidant defense mechanisms. Studies in animal models and cultured human cell lines suggest that supplementation with natural antioxidants, including vitamin C, vitamin E, lycopene, and alpha-lipoic acid, may be beneficial in suppressing the destructive effect of free radicals and improving fracture healing.\(^1,2\)

An essential component of the bone healing process, the initial inflammatory phase that occurs at the time of fracture involves the release of prostaglandins from cells damaged by the trauma of the fracture. Prostaglandin-induced inflammation activates the cyclooxygenase (COX)-1 and COX-2 enzymes, which play important roles in fracture repair. Although standard non-steroidal anti-inflammatory drugs (NSAIDs) might help relieve the pain associated with the fracture and subsequent inflammation, they would also inhibit the action of the COX-1 and COX-2 enzymes and, thus, delay healing. As a result, NSAIDs—including aspirin, ibuprofen, indomethacin, etodolac, meloxicam, nabumetone, and naproxen—are not recommended for...

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fracture pain relief.\textsuperscript{1,2} However, nourishing the body to reduce inflammation may accelerate healing. Natural anti-inflammatories such as vitamin C, omega-3 fatty acids and quercetin or other bioflavonoids may quiet the inflammatory process and promote healing.

**Boosting Mineral Intake**

Minerals such as calcium, phosphorous, magnesium, silicon, and zinc account for 70 percent of bone by weight. Fracture healing requires the availability of these minerals. Many patients under-consume minerals on an everyday basis, creating a mineral deficit that is exacerbated in the context of fracture. Key minerals for fracture healing include:

- **Zinc**—An estimated 200 enzymes require zinc for normal functioning. Zinc supplementation aids in callus formation and enhances production of bone protein, stimulating fracture healing.\textsuperscript{3}

- **Copper**—Copper is needed for the formation of collagen. Studies have shown that the body’s demand for both copper and zinc rises according to trauma severity.\textsuperscript{4}

- **Calcium and Phosphorus**—Calcium and Phosphorus—in the form of calcium hydroxyapatite crystals—are the main minerals in bone. Calcium hydroxyapatite plays a critical role in regulating the elasticity and tensile strength of bone.\textsuperscript{6} The reparative and remodeling phases of fracture healing require adequate supplies of both calcium and phosphorus, which can be obtained first from bone reserves and then from the diet.

Calcium is drawn from skeletal bones during the first few weeks of healing, but further repair requires dietary calcium. While very high intakes of calcium do not appear to speed fracture healing, consuming adequate calcium at the recommended daily allowance (RDA) is important.\textsuperscript{5,6} Calcium absorption is dependent on vitamin D, and studies suggest that calcium and vitamin D should be obtained in optimum daily doses for effective fracture healing.\textsuperscript{7} Phosphorus supplementation should be considered in the elderly, dieters, and those on low protein diets, as these individuals may not consume enough phosphorus to meet the needs of new bone formation.\textsuperscript{8}

- **Silicon**—Bioactive silicon plays an important role in collagen synthesis. A recent study found bioactive silicon enhances the effects of calcium and vitamin D3 on new bone formation.\textsuperscript{9}

**Getting the Right Vitamins**

While protein and minerals are the building blocks for bone, vitamins are the catalysts for many of the biochemical reactions involved in bone repair. In particular, the B vitamins, vitamin C, vitamin D, and vitamin K play vital roles in fracture healing, and should all be taken in therapeutic doses.\textsuperscript{10}

\begin{enumerate}
\item Igarashi A, Yamaguchi M. Great increase in kDa protein and osteocalcin at later stages with healing rat fractures: effect of zinc treatment. Int J Mol Med 2003;11(2):223-228.
\item Heaney RP, Nordin BEC. Calcium effects on phosphorus absorption: implications for the prevention and co-therapy of osteoporosis. J Am Coll Nutr 2002;21(3):239-244.
\item Brown SE. How to speed fracture healing. Center for Better Bones, Syracuse, NY.
\end{enumerate}
**Vitamin B6**

Vitamin B6, one of the B-complex vitamins that has been linked to fracture healing, is thought to modulate the effects of vitamin K on bone through complex biochemical pathways. Animal studies have linked vitamin B6 deficiency to more frequent fractures, as well as reduced fracture healing.

**Vitamin C**

In addition to its antioxidant and anti-inflammatory properties, vitamin C is needed for synthesis of the bone collagen protein matrix and severe vitamin C deficiency leads to unstable collagen. In rodent models, vitamin C supplementation accelerates the fracture healing process and higher vitamin C blood levels lead to stronger fracture callus formation. Vitamin C may also help to reduce the likelihood of developing complex regional pain syndrome (CRPS). In a study of 328 wrist fracture patients, supplementation with 500 milligrams per day of vitamin C reduced the incidence of post-fracture CRPS by more than fourfold.

**Vitamin D**

As the primary regulator of calcium absorption, vitamin D is critical for making calcium available for fracture healing and is an independent predictor of functional recovery following hip fracture. As far back as 1945, studies demonstrated that low vitamin D levels led to suboptimal fracture healing and supplementation with vitamin D accelerated initial fracture callus mineralization. Research has also shown that vitamin D—in conjunction with vitamin K—stimulates the transformation of fracture site mesenchymal stem cells into osteoblasts.

**Vitamin K**

Vitamin K has long been noted to have a beneficial effect on fracture healing. It plays an essential role in the biochemical processes that bind calcium to bone, and is required for proper formation of osteocalcin, a bone protein. Vitamin K also aids in conserving calcium by reducing the excretion of calcium in urine. Studies have shown that vitamin K is sequestered at the fracture site, resulting in decreased circulating vitamin K levels, and the time needed for vitamin K blood levels to return to normal is influenced by fracture severity.

**A Multi-Nutrient Approach to Fracture Healing**

Since bone is a complex tissue that requires many nutrients, supplementation with a wide range of key bone nutrients is likely to provide more effective support for fracture healing than individual nutrient supplementation. Several studies have found that multi-nutrient therapy accelerates fracture healing and reduces complications:

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1. Reynolds TM. Vitamin B6 deficiency may also be important. Clin Chem 1998;44:2555-2556.
In one clinical study, hip fracture patients who were given complex multi-nutrient supplementation containing carbohydrates, protein, amino acids, sodium, potassium, calcium, magnesium, chloride, trace minerals, and fat-soluble vitamins had a 15 percent rate of complications, as compared to a 70 percent rate of complications among non-supplemented hip fracture patients.  

In another placebo-controlled study, tibial fracture patients given a combination of vitamin B6, vitamin C, lysine and proline experienced more rapid fracture healing, with 33 percent of supplemented patients healing in 10 weeks, as compared to only 11 percent in the placebo group.

A meta-analysis of 17 clinical hip fracture trails reported that oral multi-nutrient supplementation, including nutrients such as carbohydrates, protein, zinc and antioxidants, reduced hip fracture-related mortality, and complications by nearly 50%.

Meeting the Nutritional Needs of Fracture Patients

Forté Elements is pioneering the development of condition-specific combinations of vitamins, minerals, amino acids, and other nutrients to support recovery and revitalization. To that end, Forté Elements has developed a multi-nutrient, Mediceutical-grade Fracture Drink that helps create a health-promoting internal biochemical environment which conserves bone-building minerals and proteins and supports fracture healing.

In addition to a combination of vitamins, minerals, amino acids, and trace elements shown to accelerate fracture healing, the Forté Elements Fracture Drink contains quercetin—a phytoflavonoid with antioxidant and anti-inflammatory properties—which also seems to have a synergistic effect with vitamin C in reducing fracture-related pain. The drink also contains bromelain, a proteolytic pineapple enzyme, which has shown value in reducing inflammation, edema and pain in fracture patients.

Forté Elements Fracture Drink

The Forté Elements Fracture Drink may be combined with a physician- or physical therapist-prescribed regimen of joint loading, range of motion and other exercises to accelerate fracture healing and return to function. Bone tissue responds to patterns of joint loading by increasing matrix synthesis, as well as altering its composition, organization, and mechanical properties. Evidence indicates that this holds true for bone under repair, as well. In addition, exercise enhances circulation, increasing the flow of nutrient-replenishing blood to the fracture site.

The multi-nutrient support provided by the Forté Elements Fracture Drink provides the essential protein, natural antioxidants and anti-inflammatories, minerals, and vitamins needed for fracture healing, and may even be useful in preventing future fractures by ensuring bone health and integrity.

References:
What is a Mediceutical?

A Mediceutical is a pharmaceutical-grade nutritional support system designed for a specific medical condition using clinically proven ingredients that are based on published science. In conjunction with licensed physicians, Forté Elements has defined and developed rigorous standards for the emerging Mediceutical category.

In order to meet the criteria for a Mediceutical, a nutritional supplement must:

1. Be formulated to support a specific health condition or situation
2. Contain only non-synthetic, pharmaceutical-grade ingredients that are Generally Recognized as Safe (GRAS)
3. Contain elements that have been validated by clinical research for the specific health condition or situation, as published in peer-reviewed journals
4. Conform to pharmaceutical-grade dosage standards for the specific health condition or situation
5. Be produced in FDA-compliant manufacturing facilities using pharmaceutical-grade manufacturing practices
6. Product has a Certificate of Analysis available confirming that product ingredients meet the Mediceutical standard and are as listed on the product label.

### Supplement Facts

<table>
<thead>
<tr>
<th>Amount Per Serving</th>
<th>% Daily Value*</th>
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<tbody>
<tr>
<td>Calorie</td>
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- **Vitamin A (Beta-Carotene and Ascorbate)** 3000 IU 70%
- **Vitamin C (Carnosic Acid)** 1500mg 150%
- **Vitamin D (Cholecalciferol)** 2000 IU 50%
- **Vitamin E (Alpha-Tocopherol)** 50 IU 167%
- **Vitamin K** (Phylloquinone) 100mcg 113%
- **Vitamin B1 (Thiamine)** 18mg 1236%
- **Vitamin B2 (Riboflavin)** 10mg 589%
- **Vitamin B3 (Nicotinic Acid)** 10mg 160%
- **Vitamin B6 (Pyridoxine)** 10mg 50%
- **Folic Acid** 400mcg 100%
- **Vitamin B12 (Cyanocobalamin)** 100mcg 1067%
- **Biotin** 100mcg 27%
- **Pantothenic Acid** 20mg 200%
- **Calcium** (Citrate, Lactate, Phosphate, Ascorbate) 1000mg 100%
- **Phosphorus** (Citrate, Phosphate) 1000mg 100%
- **Iodine** 150mcg 100%
- **Magnesium** (Hydroxide) 20mg 100%*   
- **Zinc** (Selenate) 15mg 100%
- **Copper** (Glucinate) 2mg 100%
- **Manganese** (Glucinate) 1mg 200%
- **Chromium** (Methylcobalamin) 150mcg 52%
- **Sodium** 300mg 8%  
- **Potassium** 60mg 2%  

*Percent Daily Values are based on a 2000 calorie diet. Your Daily Value may be higher or lower depending on your calorie needs.

**Supplement Facts are subject to change; please see supplement label for the most current information.

**Other Ingredients:** Ultra Pure Water, Gelatin, Beeswax (Non-GMO), Stearic Acid (Non-GMO), Maltitol, Silica, and Natural Flavors.

**Warnings:** Accidental overdose of Aspirin-containing products is a leading cause of fatal poisoning in children under 6 years of age. In case of accidental overdose, call a Poison Control Center or 911 immediately.

**This Statement has not been evaluated by the FDA. This Product is not intended to diagnose, treat, cure, or prevent any disease.**
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A fusion of science and practical medical experience unlike anything that has come before.