

Soft Tissue Calcification

Renewed Perspective on a Pathological Process

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Abstract

Soft tissue calcification (STC) is gaining recognition as a significant pathological condition that may be associated with nearly half of all chronic disease affecting the population. STC can affect organs, vessels and all other soft tissues and calcium crystals may be found in nearly every part of the body including the prostate, ovaries, bladder, ureters, kidneys, liver, retina, sclera, skin, brain, heart, muscles, joints, salivary glands, sinuses, otic nerves, spinal cord, and vessels. New advances in diagnostic imaging technology are showing that STC is integral to many common diseases and causes serious health consequences for an estimated 64,400,000 Americans. While the debate over the etiology of STC continues, recent research indicates that the primary causes of STC are 1) mineral imbalance, 2) under-potentiated inhibitors of STC, 3) smooth muscle damage, 4) infection 5) parathyroid disorder, and 6) possible genetic predisposition.^{1,2,10,11} A single approach to managing STC however, is no longer valid. In light of the accumulating research, STC is now known to be a multifactorial condition that involves 5 mechanisms: 1) macro and micro mineral balance, 2) inhibitors and promoters of calcification, 3) transporters of calcium, 4) oxidative damage, and 5) overall nutritional health. A simple and safe therapy using primarily natural ingredients can be defined by addressing the mechanism.

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Soft tissue calcification (STC) is now recognized as a significant pathological condition that may be the root cause of nearly half of chronic diseases affecting the population. Defined as the abnormal or inappropriate biomineralization of the soft tissues^{1,2} STC can affect organs, vessels, and all soft tissues. STC is known by a plurality of names and synonyms including, ectopic calcification, apatite, atheromatous plaques, biomineralization, calcified deposits, calcium phosphate, calcium salts, calculus, crystallization, hard plaque, hydroxyapatite, microcalcifications, ossification, plaque, spurs, stones, etc.

A fundamental step in the process leading to STC is the formation of calcium crystals. These crystals cause loss of soft tissue flexibility and pliability, encrust organs and vessels, and can lead to painful and lethal patient outcomes. Extensive examination of calcium crystals in vivo and in vitro has shown that these crystals also bind proteins, lipids, and other biological materials from the host media. This relationship between proteins and calcium crystals is a medical breakthrough and elucidates a new probable cause of many chronic and autoimmune diseases and conditions. For instance, it has been shown that calcium crystals induce inflammation by activation of macrophages⁵, are directly associated with a high CRP level⁹, and are found to be associated with ApoB, Fibrin, osteonectin, osteopontin, and osteocalcin and MMP-3 in atherosclerotic plaque.¹⁰

Historically, STC was considered a passive process that only involved the encrustation or adsorption of minerals to the soft tissues, for example, the endothelial lining in complex atherosclerotic lesions or cartilage in the synovial joints.^{2,3} However, recent pathologic, genetic, clinical, and biochemical evidence strongly implicates that calcium deposits are a manifestation of a complex, organized, and regulated process similar in many respects to new bone formation.^{2, 11, 12, 13} An active, cell mediated process resulting from a severe mineral imbalance and an imbalance of the promoters and inhibitors of mineralization, STC is a pathological process that is at the root of hundreds diseases and conditions.¹¹

Calcium crystals may be found in nearly every part of the body including the prostate, ovaries, bladder, ureters, kidneys, liver, retina, sclera, skin, brain, heart, muscles, joints, salivary glands, sinuses, otic nerves, spinal cord, and vessels. To date, the largest amount of

data regarding STC pertains to the calcification of connective tissues, vascular health, and excretory health, namely osteoarthritis, atherosclerosis, and kidney stones respectively. New advances in diagnostic imaging technologies (64 Slice CT, PET/CT, EBCT, etc.) are showing that STC is at the heart of greater than 50% of all chronic diseases, many of which are considered to have an autoimmune or inflammatory component.^{1, 2,3,4,5} Conditions that are directly linked to STC include some of the most chronic and expensive diseases like osteoarthritis and heart disease which affect approximately 20,000,000* and 64,400,000** Americans, respectively.

Whereas the cause of STC has been debated since its discovery in the year 1858, recent research indicates that the primary causes of STC are 1) mineral imbalance, 2) under-potentiated inhibitors of STC, 3) smooth muscle damage, 4) infection, 5) parathyroid disorder, and 6) possible genetic predisposition.^{1, 2, 10, 11, 12, 32, 39}

While there is still debate regarding the exact cause of STC, the majority of research reports that the process begins with a particle that acts as a substrate or microenvironment for the deposition of calcium phosphate.^{10, 11, 12, 14} Whether the substrate is a matrix vesicle^{11, 12, 13, 16, 17}, micro-particle¹⁵, calcifying nanoparticle¹⁴, or other “particle”, will no doubt continue to be debated, however the knowledge of how to improve patient outcomes is clear.

To date, most treatments for STC have been singular, focused therapies such as the administration of calcium carbonate or Sevelamer HCl to bind excess phosphate; or the use of parathyroid hormone replacement therapy; or even the direct and invasive procedures that remove STC deposits.

Novel therapeutic agents and combinations thereof for treating STC are under development. For instance, the use of bisphosphonates has been proposed to treat STC.⁶⁷ Other therapies utilize biological agents and proteins such as osteopontin are being researched at the present time.

A single approach to managing STC however, is no longer valid. In light of the accumulating research, STC is now known to be a multifactorial condition that involves 5 mechanisms: 1) macro and micro mineral balance, 2) inhibitors and promoters of calcification, 3) transporters of calcium, 4) oxidative damage, and 5) overall nutritional health.

* Source: National Institute of Arthritis and Musculoskeletal and Skin Diseases
** Source: American Heart Association

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A simple and safe therapy using primarily natural ingredients can be defined by addressing the mechanisms.

1. Mineral deficiency in the US is rampant. With regards to STC, one of the most important minerals is Magnesium (Mg). Magnesium, a cofactor in over 300 enzymatic processes, has been identified as a therapeutic agent to address hypertension, migraines, atherosclerosis, metabolic syndrome, and STC.¹⁸⁻²³ Research has suggested that even a slight magnesium deficiency causes the pH of bone extracellular fluid to decrease at or below the pH level of the other body fluids. This decrease makes the other body fluids supersaturated with octocalcium phosphate and this is the prime reason for calcification disorders in the soft tissues.²⁴ In the citrate form, macro-minerals such as magnesium and potassium directly inhibit crystal growth of calcium phosphate, retards spontaneous precipitation, aggregation, and crystal growth of calcium oxalate.^{27,28} Other important minerals include Calcium, Zinc, Selenium, Manganese, Chromium, and Molybdenum.

2. Inhibitors and promoters of calcification include osteocalcin and matrix GLA protein. The activity of these proteins is strictly dependent on the presence of the γ -carboxylglutamic acid (GLA) residues at a number of well defined positions. It is the GLA residue that enables these proteins to regulate many of the myriad of physiological processes controlled by Ca and to ensure the proper utilization and transport of Ca within the body.^{28, 29,30,31,35} When the carboxylic acid functionality of these proteins is not fully potentiated, these proteins do not function properly. Vitamin K2, menaquinone-7, has been shown to act as a cofactor in converting the amino acid glutamate into GLA on these proteins.^{29,33,34,35,37} Recent evidence suggests that much of the population is deficient in vitamin K. In addition, Vitamin D3 (cholecalciferol) in adequate levels with

Vitamin K2 additionally may improve bone health and keep calcium in the bones.³⁷

3. Removal of existing STC deposits is a critical component of any therapy that addresses STC. Traditional chelating and sequestering agents have been shown to bind and remove calcium phosphate crystals from the soft tissues. Compounds such as citrates^{27,38,40,41} or citric/malic acid^{42,43}, Vitamin C^{45,46}, and the synthetic amino acid EDTA are commonly used in Chelation Therapy.

4. Anti-oxidants that address reactive oxygen species (ROS) and protect cells from damaging free radicals and help prevent the oxidation of lipids in the vasculature are also important components lending healthy mineralization and endothelial or smooth muscle tissues. For example, men with even marginally low levels plasma levels of ascorbic acid were associated with a higher prevalence of coronary artery calcium.^{45,46} Pycnogenol, an extract of the Maritime Pine tree, is a powerful anti-oxidant that helps prevent the oxidation of lipids⁴⁷ and improves endothelial function^{48,49}. Other anti-oxidants that address ROSs include alpha Lipoic acid⁵⁵, tocopherol and tocotrienols, and certain of the B complex vitamins.

5. Finally, certain dietary supplement ingredients have been proven to strengthen endothelial tissues and fortify the heart and vessels and therefore provide protection from soft tissue calcification. For instance, the administration of amino acids such as taurine^{51, 52}, lysine^{53, 54}, arginine^{54, 55} and carnitine^{56, 57, 58,59} strengthen heart health and affect mitochondrial function. Other dietary supplement ingredients such as Resveratrol^{60, 61}, Quercetin^{59, 62, 63}, bromelain, curcumin⁶⁴, trypsin⁶⁵, and carotenoids such as lycopene⁶⁶ play synergistic roles in the control and prevention of soft tissue calcification.

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