The Structural Consequences of Calcium Crystal Deposition

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KEYWORDS

• Calcium crystals • Basic calcium phosphate • Calcium pyrophosphate dihydrate
• Arthritis • Vascular calcification • Atherosclerosis

KEY POINTS

- Calcium pyrophosphate dihydrate and basic calcium phosphate crystals are the most common calcium-containing crystals associated with articular and periarticular disorders.
- Common clinical manifestations of calcium crystal include acute or chronic inflammatory and degenerative arthritides and certain forms of periarthritis.
- Current evidence suggests that calcium deposition, in its various forms, contributes directly to joint degeneration and causes inflammation.

INTRODUCTION

Calcium pyrophosphate dihydrate (CPP) and basic calcium phosphate (BCP) crystals are the most common calcium-containing crystals associated with articular and periarticular disorders. Deposition of these crystals is frequently asymptomatic but it can be intermittently symptomatic. However, common clinical manifestations of calcium crystal deposition include acute or chronic inflammatory and degenerative arthritides and certain forms of periarthritis. Current evidence suggests that calcium deposition, in its various forms, contributes directly to joint degeneration and causes inflammation. Although ample in vitro and recent in vivo evidence show the potent biological effects of calcium-containing crystals, controversy still exists as to whether these crystals play a causal role or are a consequence of joint destruction.[1] Vascular calcification is a common finding in aging, diabetes, chronic renal failure, and atherosclerosis. Although arterial calcification is now accepted to be an active and highly

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regulated process similar to that of bone ossification, the level of calcification has tended to be seen as a surrogate marker for the burden of atherosclerotic disease rather than a contributor to disease progression.[2] In this regard, investigations into the size and distribution of calcified deposits in atherosclerotic plaques have suggested that small, diffuse, speckled or spotty deposits cause local plaque stress and plaque instability, whereas large platelike areas of calcification correlate with stable plaques. This article reviews the clinical, radiographic, vascular, and cellular consequences of calcium crystal deposition.

CALCIUM CRYSTAL STRUCTURE AND IDENTIFICATION

CPP crystals have rhomboid or parallelelepedic morphology. They are typically described as weakly birefringent, but it has been noted that some CPP crystals lack birefringence under polarized light microscopy (PLM).[3] Nonetheless, they are generally readily identifiable by PLM of synovial fluid.

BCP crystals are composed mostly of partly carbonate-substituted hydroxyapatite but also include octacalcium phosphate, tricalcium phosphate, and magnesium whitlockite.[4] Although BCP crystals are common, particularly in osteoarthritis (OA), their presence in synovial fluid is recognized infrequently because of the lack of a simple, reliable test for detection. BCP crystals have no features that allow identification using light microscopy. They do not show any birefringence and are therefore not visible using PLM.[5]

Individual crystals are typically less than 1 μm (20–100 nm) and aggregate in synovial fluid to form amorphous-looking clumps.[6] The most widely used stain for detecting BCP crystals is alizarin red S, which indiscriminately stains calcium-containing particulates. These particulates appear orange or red using compensated PLM. This method leads to a high rate of false-positives.[7] As a result of this, more specific methods have been used, including ^{14}C-ethane-1-hydroxy-1,1-diphosphonate binding assay and tetracycline staining.[8] BCP crystals can also be imaged using several different methods including, but not limited to, scanning electron and atomic force microscopy and Fourier transform infrared and Raman spectroscopy. These methods are limited by availability and cost.[8]

CLINICAL MANIFESTATIONS OF CALCIUM CRYSTAL DEPOSITION

Calcium crystal deposition is often asymptomatic but can be associated with a wide spectrum of clinical manifestations (**Table 1**). A more comprehensive review of diagnosis and epidemiology are presented elsewhere in this issue.

Intra-articular CPP crystals can cause pseudogout. This condition is an acute crystal-induced synovitis. It is possibly the most common cause of acute monoarthritis in the elderly.[9] Any joint may be involved, but the knees (**Fig. 1**) and wrists are the commonest sites. The attack is self-limiting.

Several provocative factors have been recognized, the most common being stress response to intercurrent illness or surgery, including lavage of the affected joint. The incidence of pseudogout following arthroscopic lavage in knee OA with preexisting chondrocalcinosis is estimated to be 26%.[10] It has also been suggested that bisphosphonates[11,12] and intra-articular hyaluronan[13] can trigger pseudogout attacks. The mechanism by which these might induce acute synovitis mediated by CPP crystals remains unclear. Other clinical presentations associated with calcium pyrophosphate dehydrate (CPPD) include OA with CPPD and chronic CPP inflammatory arthritis.[14]