

Introduction

Crystal-related arthropathies

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Historical introduction

Antoni Van Leuwenhoek was the first person to identify crystals in relation to a diseased joint. Using his early microscope he saw and drew crystals derived from the gouty tophus of a friend in 1679.¹ Sir Alfred Baring Garrod first proposed that crystals might cause inflammation; the third and fourth of his 10 propositions on gout state: 'The deposit is crystalline and interstitial ... (and) may be looked upon as the cause and not the effect of the gouty inflammation'.² His and his pupil Freudweiler then carried out the first experiments on crystal-induced inflammation at the turn of the century.³ Radiological evidence of crystalline deposits in and around the joints was noted soon after the introduction of radiology to diagnostic medicine,⁴ and reports of inflammation in relation to these deposits appeared early in the 20th century.^{5,6}

In spite of these early observations linking crystals to joint disease, the modern history of this subject is surprisingly short; many of the historical observations noted were only rediscovered when Hollander, McCarty, and others started to explore the subject in depth in the early 1960s. Examination of synovial fluids by polarised light microscopy first established that monosodium urate monohydrate crystals were a feature of gout,⁷ and then led to the discovery of calcium pyrophosphate dihydrate crystals in 'pseudogout'.^{8,9} The pseudogout syndrome was then linked with the earlier discovery of familial chondrocalcinosis by Zitnan and Sitaj.¹⁰ A rapid expansion of experimental work followed these discoveries. Crystals were shown to be capable of reproducing the acute

synovitis of gout and pseudogout¹¹ and the phlogistic properties of the crystals were demonstrated in vitro.¹² A simple, elegant model of crystal-related arthropathies emerged (Fig. 1a).

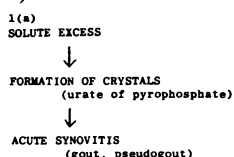


Fig. 1(a) The simple concept of crystal-related arthropathies developed in the 1960s.

During the past decade technological advances have helped produce a further expansion of knowledge, if not of understanding. Sophisticated analytical techniques have identified a far wider range of crystal species in joint tissue than was previously contemplated.¹³⁻¹⁶ In addition, the potential complexity of the interaction between crystal surfaces and biological systems has been explored,^{17,18} and the relationships between joint disease and crystal deposition have been re-examined critically.^{19,20} Consequently, present concepts of the pathways involved in a crystal-related arthropathy are less clear cut than those of two decades ago (Fig. 1b).

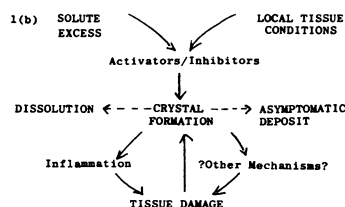


Fig. 1(b) Some of the pathways now thought to be involved in crystal-related joint disease.

Problems

The fact that crystals are often present in diseased joints is not in dispute, but the relevance of that finding is being questioned. Four fundamental problems have arisen.

(1) THE IDENTIFICATION OF CRYSTALS

Table 1 lists the increasing number of crystal species and morphologies that

Table 1 Some of the crystals identified in human articular and periarticular tissue

Monosodium urate monohydrate
Urate spherulites
Ultrasmall urate crystals
Monoclinic calcium pyrophosphate dihydrate
Triclinic calcium pyrophosphate dihydrate
Ultrasmall pyrophosphate crystals
Hydroxyapatite
Carbonate apatite
Octacalcium phosphate
Apatite spherulites
Dicalcium phosphate dihydrate
Calcium triphosphate
Calcium carbonate
Calcium oxalate
Cholesterol
Liquid lipid crystals
Mixtures of crystals

have been identified in human articular tissue. Faced with such a list and appreciating the wide range of different techniques used for tissue sampling, particle extraction, and crystal identification, the sensitivity and selectivity of the methods used must be established. Errors and artefacts are easily introduced by the methods, and it is easier to find a particle than to say either what it is or when it appeared and where it came from.

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It is almost impossible to exclude the presence of crystals in any individual patient.

(II) THE ORIGIN OF CRYSTALS

The body contains a number of complex systems designed to activate crystal formation where it is beneficial—for example, bones and teeth—and inhibit it where it is undesirable ('high risk' areas such as excretory organs contain crystal poisons—for example, salivary and urinary inhibitory proteins). Generalised or localised metabolic abnormalities may cause a solute excess that can overcome inhibition and lead to extensive crystallisation. Examples include patients undergoing haemodialysis with high phosphate concentrations who deposit calcium phosphates in a variety of sites (generalised solute excess) and patients with hyperuricaemia who develop renal stones (localised solute excess). In other crystal deposition diseases a local tissue abnormality seems to be more important than solute excess as, for example, in the dystrophic calcification developing in tuberculous lesions.

In joint diseases local or generalised solute excess may occur—for example, localised excess of inorganic pyrophosphate in pyrophosphate arthropathy and hyperuricaemia in gout. It is often difficult, however, to establish true solute concentrations because of the complexity of the biological system. Joint damage may also lead to removal of natural inhibitors of crystallisation or introduce local promoters of crystal nucleation. Small local changes in temperature, pH, and the concentration of a variety of ions could also be caused by joint damage and could promote or inhibit crystal formation.

There could therefore be complex interactions between general and local metabolic factors and localised joint damage, leading to the origin of crystal deposits.

(III) CRYSTAL-INDUCED TISSUE DAMAGE

Crystal deposition is associated with two types of joint disease: acute self limiting attacks of synovitis, and chronic destructive joint changes.

Crystal-induced inflammation is probably one of the most widely

investigated and best understood pathogenic mechanisms in rheumatic diseases. It is, however, far from being fully understood. The relevance of crystal surfaces, crystal-protein interactions, crystal-cell interactions, and the release of a variety of mediators and modulators of inflammation is still being explored.

The possible mechanisms whereby crystals might contribute to chronic destructive joint diseases have hardly been investigated. The effects of crystal-induced surface wear and of crystal deposition on the compliance and other mechanical properties of cartilage and soft tissues remain unexplored. Several recent developments, however, indicate that calcium-containing crystals may have a wider range of biological and cellular effects than was previously appreciated. They may, for example, cause release of destructive enzymes such as collagenase from synovial cells in culture, and this may be one mechanism involved in joint destruction. Rapid developments in this field may be expected.

(IV) RELATIONSHIP BETWEEN CRYSTALS AND JOINT DISEASE

Most investigators have assumed that crystal deposition is pathological and a cause of disease. There are now many reasons to doubt this basic assumption.

Figure 2 summarises some of the

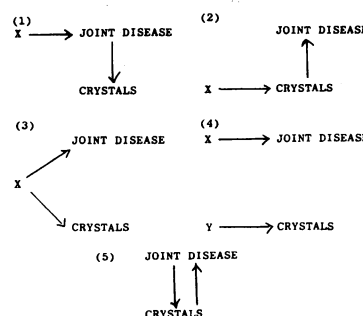


Fig. 2 Some of the possible relationships between crystal deposition and joint disease. (1) Joint disease causes crystallisation. (2) Crystals cause joint disease. (3) Crystal deposits are a by-product of the process causing arthritis. (4) Crystal deposition and joint disease are independent, and a chance relationship exists. (5) Joint damage and crystal deposition interact together.

possible relationships between crystal deposition and joint disease. Crystal deposits may be found in asymptomatic, otherwise normal, joints. Chondrocalcinosis is often a chance radiological finding, and urate crystals have recently been found free in joint fluids in the absence of any evidence of inflammation. The identification problems mentioned and the paucity of data on normal joint tissue, add to the difficulty in establishing the true relationship between crystals and joint disease.

The experimental data make a compelling case for acute synovitis being 'caused' by crystals in some patients. It remains to be seen why this does not always happen and what limits attacks. The relationship between chronic joint damage and crystals may be revealed by careful prospective studies of patients, and may depend on interactions between tissue damage and crystallisation.

Conclusions

Crystal deposition is a feature of many acute and chronic disorders of joints. The mechanisms involved have been explored only in the past 20 years. Improved technology has led to the identification of many new crystals and many new problems. The proceedings of this symposium indicate our ideas, and some of the main subjects for research in 1982. We expect that this work will soon be outdated by further advances.

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