Chondrocalcinosis in primary hyperparathyroidism

Influence of age, metabolic bone disease, and parathyroidectomy

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SUMMARY   Chondrocalcinosis is known to be common in hyperparathyroidism. In order to discover the effect of parathyroidectomy on chondrocalcinosis and to investigate this association further, we studied two groups of patients. In one group were 41 postparathyroidectomy patients, and in the other 100 admissions to the acute geriatric unit. The total incidence of chondrocalcinosis in the parathyroidectomy group was 32%, and in the elderly control group 11%. There was little or no osteoarthrosis in these patients. It was found that chondrocalcinosis occurred in the normal population from the age of 75 and in the hyperparathyroid group from the age of 45. In both groups the incidence rose steadily with age. In the hyperparathyroid group alone, preoperative serum calcium levels were no different in those with and those without chondrocalcinosis, suggesting that hypercalcaemia alone is not a sufficient stimulus for chondrocalcinosis. Those with chondrocalcinosis had higher mean preoperative alkaline phosphatase levels, nearly twice as much radiological bone disease, and were older. Parathyroidectomy had no effect on attacks of pseudogout or on preexisting cartilage calcification. A connection with high levels of circulating parathyroid hormone is suggested, and a link with physical age-related changes in cartilage postulated.

Hyperparathyroidism is known to be associated with both radiological evidence of articular chondrocalcinosis and with clinical attacks of acute calcium pyrophosphate dihydrate crystal synovitis (pseudogout). Several case reports and series of cases have been published since 1960 and the literature has been recently reviewed (Hamilton, 1975). The reported incidence of chondrocalcinosis associated with hyperparathyroidism has varied from 18% (Dodds and Steinbach, 1968) and 24% (Rickewaert *et al.*, 1966) to 40% (Glass and Grahame, 1976), but little is known of the factors which determine whether a patient with hyperparathyroidism will develop calcium pyrophosphate crystal deposition disease. Persistance of chondrocalcinosis (Zvaifler *et al.*, 1962) and attacks of pseudogout (Zvaifler *et al.*, 1962; McCarty and Silcox, 1973) after parathyroidectomy have been reported, and Glass and Grahame (1976) also have concluded that parathyroidectomy has no effect on chondrocalcinosis. There are, however, few published data to confirm this.

We report the results of a retrospective survey of patients who underwent parathyroidectomy for primary hyperparathyroidism over a 15-year period.

We examined the effect of operation on both the radiological appearance of the chondrocalcinosis and the frequency of attacks of pseudogout. In order to assess the incidence and factors predisposing to chondrocalcinosis in the normal situation, a simultaneous survey of an elderly hospital population was also undertaken.

Material and methods

Hospital records showed that 80 parathyroidectomies were performed between 1960 and 1975. 41 patients were included in our survey. Of the remainder, 18 had died, 18 had left the area or were untraceable, and 3 did not wish to participate. Detailed case histories were obtained from all 41 patients, with special reference to musculoskeletal complaints before and after operation, and all had a full general medical examination. Serum calcium, phosphate, alkaline phosphatase, urea, and electrolytes were determined on random venous blood samples using an AA4 autoanalyser, and serum parathyroid hormone levels were measured by immunoradiometric assay (Addison *et al.*, 1971). Anteroposterior x-rays of the hands, wrists, and knees and lateral views of the knees were taken using

Ilford Rapid R film. X-rays of the hands were examined for evidence of metabolic bone disease and chondrocalcinosis of the triangular cartilage of the wrist or other joints, all being assessed by a single consultant radiologist. X-rays of the knees were examined for the presence of chondrocalcinosis and degenerative changes in the tibiofemoral compartments.

In those patients who had undergone parathyroidectomy at least one year before attending for follow-up, the postoperative x-rays of the hands, wrists, and knees were compared with the preoperative x-rays whenever possible. These were also studied for metabolic bone changes associated with hyperparathyroidism. In some cases skeletal surveys were available, but in many only hand x-rays could be traced. When no preoperative films were available for comparison, serial postoperative x-rays of the hands, wrists, and knees, separated by an interval of at least 3 years, were assessed for changes which might have occurred as a result of removal of the tumour.

For the survey of the control group, 100 unselected admissions to the acute geriatric unit in this hospital were chosen. The only exclusions were those patients who were too ill to co-operate, or who had leg amputations. Serum calcium and alkaline phosphatase were measured. X-rays were limited to the knee joints, as Ellman and Levin (1975) have shown that if a patient has chondrocalcinosis x-rays of the knees alone will detect 99% of cases. Anteroposterior x-rays of both knees were taken, using a portable Dean MX4 camera and Ilford Rapid R film. The processing, techniques, and personnel were similar to those in the first survey.

The degree of osteoarthrosis was graded as follows. None, which included spiking of the tibial tubercles; mild or moderate, indicating increasing degrees of loss of articular cartilage, sclerosis, and osteophyte formation; and severe, equivalent to complete loss of articular cartilage with gross deformity. The degree of osteoarthrosis was classified according to the changes recorded in the worst affected compartment. Statistical analysis, where appropriate, was carried out using Student's 't' test (unpaired means).

Results

Thirteen out of the 41 patients examined in the survey were found to have radiographic evidence of chondrocalcinosis, an incidence of 32% (Table 1). 3 patients with chondrocalcinosis gave a history of acute pain and swelling in at least one of the affected joints, but no one in the group without chondrocalcinosis had ever suffered an attack of acute arthritis. The clinical details of these patients are given in Table 2. Only one patient (Case 9) described attacks of acute arthritis in an affected joint before operation but at the time of interview, 2 years after removal of a parathyroid adenoma, she remained symptom free. Although the synovial fluid was not examined for crystals, her serum uric acid was normal and she may be classified as having 'probable' pseudogout (McCarty, 1966). The other 2 patients developed acute arthritis in the radiologically affected joints for the first time after removal of the parathyroid tumour.

It was only possible to compare current x-rays with those taken previously in 10 of the 13 patients with chondrocalcinosis. Of the other 3 patients, one died soon after operation, one had the operation postponed indefinitely, and one has undergone parathyroidectomy within the last 6 months and therefore too soon for inclusion in this review.

Preoperative x-rays of the hands and/or knees

Table 1 *Details of patients with chondrocalcinosis*

Case no.	Sex	Age at operation	Date of operation	Previous chondrocalcinosis							Chondrocalcinosis 1975						Observed change	Reason for no comparison
				Knees		Wrists		Other		Date of x-ray	Knees		Wrists		Other			
				L	R	L	R	L	R		L	R	L	R	L	R		
1	F	68	1960	−	−	+	+	−	−	1972	−	−	+	+	−	−	None	
2	F	52	1962	0	0	0	0	0	0	—	+	+	+	+	−	−	(None)*	
3	F	66	1970	+	+	+	+	+	+	1972	+	+	+	+	+	+	None	
4	F	65	1971	0	0	−	−	−	−	1971	+	+	−	−	−	−	(None)*	
5	F	66	1972	0	0	−	−	0	0	Pre-op	+	+	−	−	−	−	(None)*	
6	F	72	1972	+	+	+	+	−	−	1972	+	+	+	+	−	−	None	
7	F	65	1972	+	+	+	+	−	−	1972								Died after operation
8	F	55	1973	+	+	−	−	−	−	1973	+	+	−	−	−	−	None	
9	F	65	1973	0	0	−	−	0	0	1973	+	+	−	−	−	−	(None)*	
10	F	48	1974	+	−	−	−	−	−	Pre-op	+	+	−	−	−	−	None	
11	F	(71)	No op								+	+	+	+	−	−		Operation postponed
12	M	41	1975	0	0	0	0	+	+	Pre-op	+	+	+	+	+	+	None	
13	F	68	1976	0	0	0	0	0	0		+	+	−	−	−	−		Too soon for assessment

+ =radiological calcification; − =no calcification seen; 0=no x-rays available.
*Insufficient numbers of x-rays available for a complete comparison.

were available for comparison with post-operative films in 3 patients. In the other 7 patients serial post-operative x-rays taken at intervals of at least 3 years were compared. The presence of chondrocalcinosis was recorded (Table 1). In no patient was a significant change observed in the degree of chondrocalcinosis, although in 4 cases the earlier x-rays were not complete enough to allow a full comparison to be made.

Table 2   *Details of 3 patients with pseudogout*

Case no.	Sex	Age	Date of operation	Date of episode	Joints affected	Crystals
4	F	70	1971	1974	L knee	Not looked for
9	F	50	1974	1972/3	L knee (x3)	Not looked for
12	M	44	1975	1975/6	R ankle	MSU
					L knee	CPPD

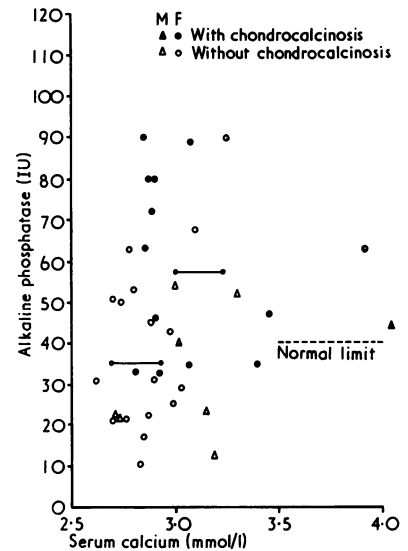MSU = monosodium urate;
CPPD = calcium pyrophosphate dihydrate.

Fig. 1   *Preoperative values of serum alkaline phosphatase against serum calcium in 41 patients (males and females) with hyperparathyroidism. Horizontal lines indicate mean values. Conversion: SI to traditional units—Calcium: 1 mmol/l ≈ 4 mg/100 ml.*

In an attempt to detect factors which might predispose to the development of chondrocalcinosis, the biochemical and radiological data of those with chondrocalcinosis were compared with those without (Tables 3 and 4). It was found that patients with articular cartilage calcification were significantly older at the time of operation and had a significantly higher preoperative serum alkaline phosphatase than patients without cartilage calcification, but chondrocalcinosis did not correlate with the preoperative serum calcium levels or tumour histology, nor was there any relationship between preoperative serum alkaline phosphatase and serum calcium levels (Fig. 1).

Although complete skeletal surveys before surgery were not always done, x-rays of the hands and skull were available. Patients with chondrocalcinosis showed evidence of periostitis, osteitis fibrosa cystica, or 'pepperpot skull' more frequently than those without. The figures are given in Table 3. After operation the serum calcium, alkaline phospha-

Table 3   *Age and radiological and biochemical details of 41 patients with and without chondrocalcinosis (CCA) before operation*

	n	Sex ratio		Age (mean±SD)	Serum Ca^{++} (mmol/l) (mean±SD)	Alkaline phosphatase (IU) (mean±SD)	Radiological bone disease
With CCA	13	12F	1M	61±9·0	3·05±0·34	57±22·46	6/13 (45%)
Without CCA	28	19F	9M	44±13·6	3·03±0·35	41±26·78	7/28 (25%)
Significance				P<0·01	NS	P<0·05	

Conversion: SI to traditional units—Calcium: 1 mmol/l ≈ 4 mg/100 ml.

Table 4   *Histology of resected parathyroid gland in 41 patients*

	n	Adenoma	Carcinoma	Hyperplasia	NAD	Not known
With CCA	13	9	0	2	1	1
Without CCA	28	18	2	3	2	3
Total	41					

NAD = no abnormality detected.

tase, and parathormone levels, when available, returned to normal in all patients except in the 2 with recurrent parathyroid carcinoma.

The sex ratio of the whole group was male to female 1:3. However, the ratio in the patients with chondrocalcinosis was 1:12, due to the preponderance of postmenopausal women with hyperparathyroidism. This has been previously described (Muller, 1969) (Table 3, Fig. 2).
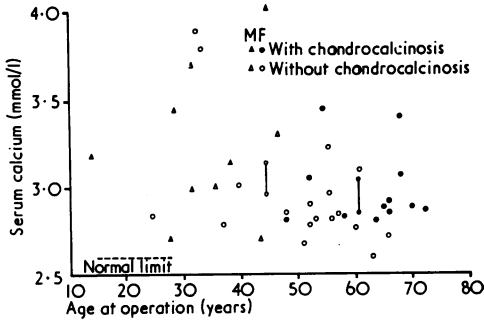
Fig. 2 *Age at operation against preoperative serum calcium levels in 41 patients with hyperparathyroidism. Vertical lines indicate mean values.*

In the control group survey of 100 unselected admissions to the acute geriatric unit (32 males, 68 females) chondrocalcinosis was found in 5 men (15%) and 6 women (9%), giving a total in the group of 11%. In every case calcification was seen in all four menisci in anteroposterior views of the knees. When the radiographs were classified by degenerative disease, ie. none, mild, moderate, and severe as described above, it was found that 9 out of 11 cases of chondrocalcinosis occurred in the 'none' or 'mild' groups (Fig. 3). The average age of the patients in this group with chondrocalcinosis was 82 years ($\pm 6 \cdot 68$ SD) and those without, 76 years ($\pm 6 \cdot 34$ SD). The difference was significant ($P < 0 \cdot 05$). Serum calcium and alkaline phosphatase levels were normal.
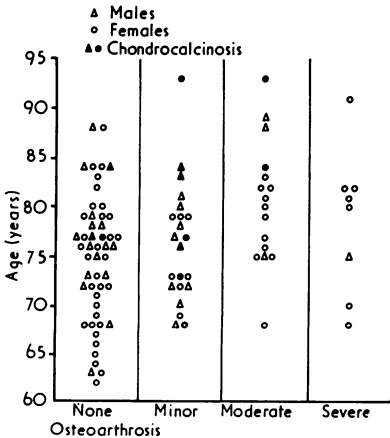

Fig. 3 *100 patients in the normal survey, divided into four columns according to the degree of radiological osteoarthrosis.*

Fig. 4 shows both the incidence and the relative cumulative frequency of chondrocalcinosis in the groups taken at 5-year intervals, for both the hyperparathyroid group and the normal population survey. While tabulating the true incidence by age group shows clearly the absence of chondrocalcinosis in the younger age groups, the numbers are too small and the distribution therefore too sporadic to show the influence of increasing age. The cumulative frequency allows greater numbers to be considered, as each column represents all the patients over any particular age limit. The result is that the incidence of chondrocalcinosis rises sharply as the lower age limit of the group is raised, showing that the age of the patient is a strong predisposing factor to the appearance of chondrocalcinosis in both the hyperparathyroid patients and in the normal survey.
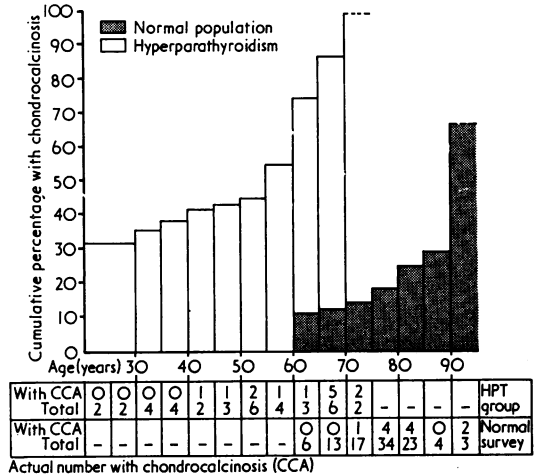

Age(years)	30		40		50		60		70		80		90		
With CCA	0	0	0	0	1	1	2	1	1	5	2	–	–	–	–	HPT
Total	2	2	4	4	2	3	6	4	3	6	2	–	–	–	–	group
With CCA	–	–	–	–	–	–	–	0	0	1	4	4	0	2	Normal
Total	–	–	–	–	–	–	–	6	13	17	34	23	4	3	survey

Actual number with chondrocalcinosis (CCA)

Fig. 4 *Age relationship of patients in both groups with chondrocalcinosis. The top figure in the boxes shows the relative cumulative frequency of chondrocalcinosis, and the lower figure the actual number of patients involved, both at 5-year intervals. HPT=hyperparathyroidism.*

Discussion

In the literature the incidence of chondrocalcinosis in both the normal population and in hyperparathyroidism varies considerably. In the normal population, for example, the figures range from 27·5% (Ellman and Levin, 1975) to 5·6% (McCarty *et al.*, 1966). In patients with hyperparathyroidism, Dodds and Steinbach (1968) found an incidence of 18%, while Glass and Grahame (1976) reported 40% in their series of postparathyroidectomy patients. Our results for both groups lie in the middle of the range;

but clearly there must be an explanation for the wide discrepancies.

By far the most important factor is the age range of the survey concerned. Fig. 4 shows that the frequency of chondrocalcinosis rises steeply with age, and therefore it is to be expected that the incidence in a whole adult population study such as McCarty's cadaveric survey will be much lower than that of Ellman and Levin (1975) or Bocher *et al.* (1965) both of which were conducted in an old people's home. A second factor is the grade of film used. The unexpectedly high figures of Ellman and Levin were due to the use of ultrasensitive industrial film, which shows calcification which cannot be seen on standard grade x-ray film. It is then essential when comparing one survey with another that the age range is defined and standard x-ray film used.

In none of the patients for whom sequential joint x-rays were available was there any detectable change in the degree of cartilage calcification. This suggests that once calcification occurs it is independent of parathyroid activity. As pseudogout is thought to result from calcium pyrophosphate crystals leaching out from the articular cartilage (Bennett *et al.*, 1976), it is not surprising that parathyroidectomy has no effect on attacks of pseudogout either. Pseudogout was in fact uncommon in our experience, occurring in 3 out of the 13 patients with chondrocalcinosis in the hyperparathyroidism group and not at all in the normal population, an overall frequency of 12·5%. None of the attacks occurred in the immediate postoperative period, when patients with chondrocalcinosis are very liable to attacks of acute crystal synovitis (O'Duffy, 1973; Bilezikian *et al.*, 1973), but one patient did develop acute monosodium urate arthropathy during this period.

The sex ratio of patients with chondrocalcinosis in the two groups was widely different. In the control population the ratio was male to female 5:3, whereas in the hyperparathyroidism group the ratio was 1:12. The reason that virtually no males in the hyperparathyroidism group developed chondrocalcinosis is because all the patients over 50 in the group were female (see Fig. 2.)

The factors influencing the development of chondrocalcinosis are complex. Fig. 3 shows that when the two groups of patients are considered as a whole, the presence of hyperparathyroidism accelerated the appearance of chondrocalcinosis by several decades, but in the hyperparathyroid group alone the serum calcium levels were no different in those patients with and without chondrocalcinosis (Table 3). Thus hypercalcaemia alone is unlikely to be a sufficient stimulus to chondrocalcinosis.

The two hyperparathyroidism subgroups did however differ in both age and preoperative serum alkaline phosphatase levels. It is well known that radiologically manifest bone disease in hyperparathyroidism is associated with high alkaline phosphatase levels. However, radiology is a very insensitive way of detecting bone disease in this situation, as the changes have to be severe before being radiologically detectable. High normal and mildly abnormal alkaline phosphatase levels are common in hyperparathyroidism. Gallagher and Nordin (1972) showed that oestrogen therapy not only lowered the urinary calcium and hydroxyproline excretion rates in postmenopausal hyperparathyroidism but serum alkaline phosphatase levels as well. This suggests that serum alkaline phosphatase is a reasonable indicator of active bone disease in this condition, and is a useful indicator of bone disease which is not severe enough to show on x-rays.

Dodds and Steinbach (1968) stated that metabolic bone disease was more common in patients with chondrocalcinosis, a result that we can confirm not only radiologically, but now biochemically as well. This association can be taken a stage further. O'Riordan *et al.* (1972) measured parathyroid hormone levels in hyperparathyroid patients and found that those with radiologically apparent bone disease had much higher levels of parathormone and larger tumours than those with uncomplicated disease, but in fact serum calcium levels were often no higher than in patients without bone disease (J. S. Woodhead, personal communication, 1976). By inference, therefore, patients with chondrocalcinosis should have higher parathyroid activity than those without but without necessarily higher serum calcium levels. Either raised alkaline phosphatase levels or parathyroid hormone may therefore play a part in the development of chondrocalcinosis. However, we were unable to measure this directly, as most patients had operations before parathyroid hormone levels were routinely measured in this area.

Fig. 4 shows the influence of age in the development of chondrocalcinosis, where the incidence of disease in both groups of patients rises steadily with increasing age. The fact that this is true in the normal population suggests that age, or a factor directly related to age, is of fundamental importance in the development of cartilage calcification. However, other factors such as the physiochemical aspects of cartilage calcification should be considered. Benderly and Maroudas (1975) found the ionic concentration of calcium and phosphate in cartilage in equilibrium with physiological Ringer's solution to be unexpectedly high, and that cartilage is in fact supersaturated with respect to calcium and phosphate in the normal state. It is of more interest then to consider why cartilage does not calcify spontaneously, rather than why it does so under certain conditions.

Spontaneous precipitation may be prevented by two mechanisms. First the activity coefficient of calcium ions in cartilage is low (Benderly and Maroudas), which is presumably due to the gel-like structure of cartilage inhibiting ionic mobility, and second proteoglycans actively inhibit calcium pyrophosphate crystallization (Howell *et al.*, 1969). It follows that once the calcium pyrophosphate had crystallized out, it would still be in equilibrium with a supersaturated solution and therefore be unable to redissolve. It might in fact be expected to increase even in the presence of normal serum calcium levels; chondrocalcinosis therefore is permanent.

If spontaneous calcification is prevented by the physical structure of the cartilage, then deterioration of this structure would conversely allow crystallization to take place. The incidence of calcification rises steadily with age, suggesting that age-related physical changes in the cartilage structure might be responsible. Such physical changes probably exist in view of the deteriorating performance of cartilage with increasing age, e.g. the reduction of tensile stiffness and fracture stress in older cartilage (Kempson, 1975), but these changes have not so far been clearly shown. A gradual deterioration in inhibition would fit our findings well, as such inhibition would be overcome earlier by a high cartilage calcium concentration than a normal one.

We have studied two groups of patients, one with hyperparathyroidism, the other an elderly hospital population, and found that chondrocalcinosis was common in both. There was a strong age relationship in both groups. The majority of patients were asymptomatic, and pseudogout was rare. However, neither cartilage calcification nor attacks of pseudogout were influenced by parathyroidectomy, and it was found that patients with hyperparathyroidism developed chondrocalcinosis at a much earlier age than did the control population. It was shown that in the hyperparathyroidism group those with and those without chondrocalcinosis differed in age and serum alkaline phosphatase levels, but not in serum calcium levels. There is a possible age relationship based on the physical structure of cartilage.

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