

# Significance of crystals in patients with osteoarthritis of the knee joint

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## ABSTRACT

To identify the relation between the presence of calcium pyrophosphate dihydrate crystals (CPPD) and clinical, laboratory, and radiographic findings in patients with osteoarthritis of the knee joint, an analytical study was done in 2001, which included 100 patients with osteoarthritis of the knee joint. Synovial fluid analysis with the examination of a wet preparation under polarized microscopy was conducted for each patient. The study included a comparison between CPPD positive patients and those who are negative for these crystals. CPPD crystals were identified in 48% of the patients. The study shows a significant association of CPPD crystals with genu-valgum deformity, limited flexion and extension, elevated erythrocyte sedimentation rate (ESR) and cloudy inflammatory synovial fluid with poor viscosity. We concluded that CPPD deposition is associated with more disabling and deforming arthritis of the knee joint. Clinical criteria are needed to identify patients with occult CPPD deposition disease.

## الخلاصة

أجرينا سنة ٢٠٠١ دراسة لمائة مريض لديهم سوفان مفصل الركبة بهدف توضيح علاقة وجود بلورات بايروفوسفات الكالسيوم ثنائية الماء في السائل المفصلي من عدمه تجاه الحالة السريرية والشعاعية والفحوص المختبرية. أجرينا فحص السائل المفصلي بحالته الرطبة بالمجهر الاستقطابي ولكافة الحالات التي شملتها الدراسة. وجدت البلورات لدى ٤٨% من المرضى.

أثبتت الدراسة وجود علاقة إحصائية ذات مغزى بين كل من حالات الركبة الروحاء وتحدد بسط وثني حركة الركبة وارتفاع سرعة تفاعل الدم وتكدر أو خمج أو قصور لزوجة السائل المفصلي ووجود بلورات بايروفوسفات الكالسيوم ثنائية الماء. نستنتج أن ظهور أو ترسب هذه البلورات يرافق السوفان المفصلي الشديد الوطأة والمشوه لمفصل الركبة. وإن وضع مؤشرات سريرية لتمييز من لديهم بلورات غير منظورة ممن ليس لديهم بلورات جدير بأن يحقق.

The nature of the relation between osteoarthritis and the various forms of calcium crystals including calcium pyrophosphate dihydrate crystals "CPPD" continue to challenge researchers. The basic question is whether such crystals are directly relevant to the development of osteoarthritis or are merely byproducts or markers of the disease itself<sup>(1)</sup>. Osteoarthritis is a major cause of locomotor pain and an important health care challenge<sup>(2)</sup>. Previously considered a boring "wear and tear", "degenerative" disease that must be accepted as the inevitable consequence of trauma and aging, osteoarthritis is now increasingly viewed as a dynamic, essentially reparative process with potential for health intervention and prevention<sup>(3)</sup>.

Crystal associated arthropathies can be accompanied by dramatic morbidity. Even when patients are asymptomatic, the presence of crystal deposits in joints can gradually lead to degenerative disease and disability<sup>(4)</sup>. In CPPD deposition disease, the most significant clinical pattern is an acute arthritis, mostly of the knee joint, the so-called pseudogout syndrome. CPPD deposition disease can blend mechanical illness and inflammatory flare<sup>(5)</sup>. When the X-rays are normal or display osteoarthritis, synovial fluid analysis with examination of a wet preparation under polarized microscopy provides unique and valuable information about what is going on inside the joint<sup>(6)</sup>.

The aim of this work is to study the significance of "CPPD" crystals in patients with acute knee pain who fulfill the

American College of Rheumatology (ACR) classification criteria of osteoarthritis of the knee joint "clinical and radiological"<sup>(7)</sup>, and to identify the relation between the presence of CPPD crystals and the clinical, laboratory and radiographic findings.

## PATIENTS AND METHODS

A case-series study (prospective) with an analytical method is conducted in Ibn-Sina teaching hospital in Mosul, which includes the collection of 100 patients with acute knee pain who, fulfil the ACR criteria of osteoarthritis. This study also consists of a comparison between patients who are positive for CPPD crystals and those who are negative. A detailed history was conducted for each patient in addition to the clinical examination. All patients were sent for ESR and X-ray of the knee joint. Grading of osteoarthritis of knee joint according to radiological findings was done depending on Kellegren and Lawrence grading scheme.

The investigator conducted aspiration of the knee joint and synovial fluid analysis. A wet preparation was then examined using ordinary light microscope and polarized light microscope "Ziess" supplied by two retardation plates searching for CPPD crystals. Standard descriptive statistics method was used to describe patients. The statistical analysis of data was carried out using the chi square test of independence for testing the significance of difference between CPPD positive group and CPPD negative group. The relative risk estimate (odds ratio) is obtained for the variables.

## RESULTS

A total of 100 patients suffering from acute knee pain and swelling who fulfil the ACR classification criteria of osteoarthritis of the knee joint "clinical and radiological" were considered to represent the study sample.

The female patients represent 64% with male to female ratio 0.56: 1, and the mean age of the study sample was  $(56.6 \pm 7.74)$ .

CPPD crystals were identified in 48% of patients. Descriptive analysis of the study sample is shown in (Table 1).

Out of the one hundred patients, 87 patients were included in the comparative study and 13 patients who proved to have specific unrelated disorders were excluded regardless of the presence or absence of crystals. 43 patients represented the CPPD

positive group "CPPD+" while 44 patients represented the CPPD negative "CPPD-". The comparative study was conducted between these two groups.

The comparative study shows a highly significant association between CPPD crystals and constitutional symptoms associated with acute knee pain ( $P \leq 0.005$ ). A highly significant association ( $P \leq 0.001$ ) with odds ratio 10.14 was also observed between CPPD+ patients and joints complaint other than the knee joints.

Table (2) shows a significant association between CPPD crystals and diabetes mellitus. ( $P \leq 0.032$ ) with an odds ratio of 4.14. Furthermore, the study shows no significant association between presence of CPPD crystals and the history of previous local steroid injection, previous trauma, or family history of knee joint involvement.

It was shown that increased joints warmth had a highly significant association with CPPD crystals in our study sample. ( $P \leq 0.0001$ ) with an odds ratio of 41.05. The study shows a highly significant association between CPPD crystals and genu valgus deformity. ( $P \leq 0.006$ ) with an odds ratio of 7.22. The study also reveals a highly significant association between CPPD crystals and limited joint flexion compared with CPPD- patients. ( $P \leq 0.008$ ) with an odds ratio of 6.83. Also a significant association was observed between CPPD crystals and limited joint extension  $> 10^\circ$ . ( $P \leq 0.05$ ) with an odds ratio of 3.13. No significant association was shown between CPPD crystals and genu varus deformity.

The study reveals a highly significant association between CPPD crystals and cartilage calcification. ( $P \leq 0.002$ ) with an odds ratio of 9.32. As shown in (Table 2), 30.2% of CPPD+ patients had cartilage calcification compared with 4.5% in CPPD- patients. The study shows no significant association between CPPD deposition disease and grade III-IV osteoarthritis or patello-femoral osteoarthritis of the knee joint.

The study shows a highly significant association between CPPD deposition disease and E.S.R  $> 40$ . Synovial fluid analysis reveals a highly significant association between CPPD deposition disease and cloudy, inflammatory fluid with poor viscosity with ( $P \leq 0.0001$ ) and an odds ratio of (41.05), (39.2), (29.17) for them respectively.

**Table (1): Descriptive analysis of the study sample.**

Information	%
Previous history of acute knee pain "same joint"	64%
History of local steroid injection "same joint"	28%
History of joint aspiration "same joint"	17%
History of previous trauma "same joint"	16%
Diabetes Mellitus	15%
Limited Flexion	87%
Genuvarus deformity	41%
Limited extension > 10°	34%
Genuvalgus deformity	13%
Grade III - IV osteoarthritis of knee joint	60%
Patello-femoral osteoarthritis	50%
Cartilage calcification of affected joint	15%
ESR ≥ 40mm/hr	31%
Total WBC count ≥ 11.000 × 10 <sup>9</sup> /L	7%
Inflammatory synovial fluid	43%
Synovial fluid with poor viscosity	38%
Cloudy synovial fluid	33%

**Table (2): The association between the presence of CPPD crystals and the clinical, laboratory and radiographic findings**

Finding	CPPD+ n = 43	CPPD- n = 44	X <sup>2</sup>	P-value	OR
Constitutional Symptoms.	37.2%	11.4%	7.933	≤0.005	4.62
Involvement of other joints	32.6%	4.5%	11.37	≤0.001	10.14
Diabetes mellitus.	23.6%	6.8%	4.623	≤0.032	4.14
Previous trauma "same joint"	23.6%	13.6%	1.341	N.S	1.92
Previous local injection	34.9%	20.5%	2.267	N.S	2.08
Family history of acute knee pain	39.5%	32.6%	0.007	N.S	1.04
Increase joint warmth	48.8%	2.3%	24.958	≤0.0001	41.05
Genuvalgus deformity.	25.6%	4.5%	7.572	≤0.006	7.22
Limited Flexion.	95.3%	75%	7.085	≤0.008	6.83
Limited extension > 10°	37.2%	15.9%	5.177	≤0.025	3.13
Genuvarus deformity	34.9%	59.3%	2.749	N.S	0.49
Cartilage calcification.	30.2%	4.5%	10.057	≤0.002	9.32
Osteoarthritis grade III-IV	62.8%	75%	2.041	N.S	0.56
Patello-femoral osteoarthritis.	55.8%	56.8%	1.587	N.S	0.96
ESR > 40 mm/hr	37.2%	9.1%	9.712	≤0.002	5.93
Cloudy Synovial Fluid	48.8%	2.3%	24.958	≤0.0001	41.05
Inflammatory synovial fluid	65.1%	4.5%	35.316	≤0.0001	39.2
Poor viscosity	58.1%	4.5%	29.185	≤0.0001	29.17

## DISCUSSION

In this work, the diagnosis of CPPD deposition disease is confirmed by the demonstration of CPPD crystals by polarized light microscopy with the presence or absence of radiographic intra-articular deposits. Radiographic studies are not sensitive enough to detect early intra-articular crystal deposits. On the other hand, chondrocalcinosis may become less evident if cartilage thickness is lost<sup>(8,9)</sup>.

Thirteen patients were proved to have specific unrelated disorders. This result emphasizes the importance of the synovial fluid aspiration and analysis in effusions of unknown cause<sup>(10)</sup>.

In this comparative study, there is a significant association of CPPD associated disease with systemic manifestations, involvement of other joints, increase joint warmth, elevated ESR, and cloudy inflammatory fluid with poor viscosity. All

these are in agreement with the results of several studies, which concentrate on the clinical presentation of CPPD deposition disease<sup>(6,9,11,12)</sup>.

Significant association of CPPD deposition disease with diabetes mellitus is shown in the study. This is consistent with a study which suggested a possible association between CPPD deposition disease and diabetes mellitus<sup>(3)</sup>, the study shows significant association of CPPD deposition disease with genu-valgus deformity, limited flexion and /or limited extension of knee joint, but no significant association with genu-varus deformity. Previous studies mention such association as well as genu-varus deformity<sup>(8,11)</sup>. Cartilage calcifications were only seen in 30.2% of CPPD deposition disease and this seems to be due to: firstly, radiographs of the affected joints may not be helpful in detecting early crystal deposits. Secondly, patients were not screened for CPPD crystal deposits in other joints.

## CONCLUSION

The study has affirmed that calcium pyrophosphate dihydrate "CPPD" crystals are associated with more severe joint injury. The relationship of CPPD crystal deposition to osteoarthritis is still unclear. However, these crystals are associated with more disabling and deforming arthritis of the knee joint. Valgus deformity is highly suggestive of CPPD deposition disease.

Radiography is only marginally helpful in the diagnosis of CPPD deposition disease and the characteristic calcification may or may not be visible on radiography of involved joint; therefore synovial fluid analysis with examination of a wet preparation under polarized microscopy is an essential diagnostic procedure for CPPD deposition disease.

The following recommendations can be made:

1. Patients with acute knee pain who fulfil the American College of Rheumatology "ACR" classification criteria for osteoarthritis should be investigated for an underlying pathology before being labelled as primary "idiopathic" osteoarthritis.
2. Clinical criteria are needed to identify patients with occult CPPD deposition disease that may require more aggressive anti-inflammatory therapy than those with non-inflammatory osteoarthritis.
3. The impact of other crystals on the joint needs further studies.

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