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The Incidence and Significance of Calcium Pyrophosphate Dihydrate Deposits in Histologic Examinations of Total Hip, Knee, and Shoulder Joint Arthroplasties

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- **Context.**—The incidence, distribution, and significance of calcium pyrophosphate dihydrate deposition (CPPD) disease have not been extensively compared among various total joint resections.

- **Objective.**—To investigate and define the clinical and pathologic features of CPPD in hip, shoulder, and knee arthroplasties.

- **Design.**—We retrospectively reviewed consecutive total hip, knee, and shoulder arthroplasty cases (N = 3195) confirmed pathologically between January 1, 2017, and October 10, 2018, comparing clinical and pathologic data.

- **Results.**—Among 2004 hip arthroplasties, 61 (3%) had CPPD on pathologic examination; the majority had a histologic diagnosis of osteoarthritis followed by fracture and avascular necrosis. Of 1113 knee arthroplasties, 98 (9%) had CPPD; all had a histologic diagnosis of osteoarthritis. Among 78 shoulder arthroplasties, 10 (13%) had CPPD; all but one had a histologic diagnosis of osteoarthritis. Patients with hip and knee CPPD were significantly older than those without CPPD. Of the 169 pathologically detected CPPD cases, only 35 (21%) were documented on preoperative radiologic images or by other clinical means; radiology reports were significantly more likely to document chondrocalcinosis in the knees than in the hips. Histologically, CPPD were noted almost exclusively in the separately submitted soft tissues/joint capsule, concomitantly involving the articular cartilage surface in only 3.0% (5 of 169) of cases.

- **Conclusions.**—Calcium pyrophosphate dihydrate deposition is more than twice as likely to occur in the knees and shoulders compared with the hips. Patients with CPPD in the knees or hips are usually not recognized preoperatively/radiologically and constitute a significantly older population. Reliably establishing the diagnosis of CPPD requires pathologic examination of the submitted soft tissue/joint capsule.

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Calcium pyrophosphate dihydrate deposition (CPPD) disease is a metabolic arthritis produced by the deposition of calcium pyrophosphate (CPP) dihydrate crystals in the synovium, joint capsule, and periarticular soft tissues, including synovial fluid, of large joints and digits.1-2 Calcium pyrophosphate dihydrate deposition may complicate and arguably even cause osteoarthritis (OA)/degenerative joint disease. According to the European League Against Rheumatism CPPD Task Force, CPPD is best considered an umbrella term that encompasses acute CPP crystal arthritis, osteoarthritis with CPPD, and chronic CPP crystal inflammatory arthritis. Chondrocalcinosis, a term typically used by radiologists, generally refers to cartilage calcification, most commonly due to CPPD, involving the menisci of elderly patients.3 Rheumatologists tend to prefer the term pseudo-gout for symptomatic cases related to CPP crystal deposition. Regardless of anatomic site, terminology, or condition, for the pathologist, CPPD refers to the tissue deposition, characteristically within joints, of small rhomboid to rectangular crystals, retained by usual tissue processing and staining, typically weakly birefringent, and not generally associated with a significant histiocytic reaction.

During the past decade, we noticed that a significant number of pathologically evaluated arthroplasty cases from the shoulder, hip, and knee had CPP deposits, and that these patients were usually not recognized clinically or radiologically. Among more recent literature, the incidence, distribution, and significance of these CPP crystalline deposits have not been extensively compared and studied for different total joint resections. For these reasons, we analyzed our experience among consecutive total joint resection specimens and the diagnosis of CPPD, seeking to better define the anatomic localization (eg, articular cartilage and/or joint capsule) of the deposits, associated diagnoses, documented radiologic findings, and clinical and demographic characteristics of these patients.

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Table 1. Incidence of Calcium Pyrophosphate Dihydrate Deposition (CPPD) in Histologic Examinations of Total Hip, Knee, and Shoulder Joint Arthroplasties

| Site          | Hip      | Knee     | Shoulder |
|---------------|----------|----------|----------|
|               | Total    | CPPD     | Total    | CPPD     | Total    | CPPD     |
| Age range (mean), y | 17–102 (66) | 49–100 (73) | 38–93 (68) | 49–91 (72) | 38–85 (64) | 45–84 (67) |
| Pathologic diagnosis, No. (%) |         |          |          |          |          |          |
| OA            | 1524 | 45 (74) |          | 1113 | 98 (100) |          |
| Fracture      | 274  | 13 (21) |          | 0    | 0        |          |
| AVN           | 202  | 3 (5)   |          | 0    | 0        |          |
| Metastatic tumor | 4  | 0       |          | 0    | 0        |          |
| Total         | 2004 | 61 (3)  |          | 1113 | 98 (9)   | 78       | 10 (13)  |

Data Analysis of CPPD in Total Hip, Knee, and Shoulder Arthroplasties

Of 2004 hip arthroplasty patients (903 males, 1101 females; age range, 17–102 years), 61 (3%) had incidental CPPD. Among the 61 patients with CPPD, the majority (45; 74%) of total, 3% of 1524 OA/degenerative joint disease cases; age range, 49–100 years; mean, 73 years) had a pathologic diagnosis of OA/degenerative joint disease, followed by fracture (13; 21% of total, 5% of 274 fracture cases; age range, 50–89 years; mean, 72 years) and avascular necrosis (AVN) (3%; 5% of total, 1.5% of 202 AVN cases; age range, 55–75 years; mean, 67 years). The mean age of patients with hip CPPD was significantly older than that of those without CPPD (73 versus 66, Student t test 2-tailed P < .001). Of the 13 fractures associated with CPPD, 6 also had at least mild OA. All of these fractures were secondary to trauma and/or clinical osteoporosis, and none were related to tumor or metastatic disease. The 3 examples of AVN with CPPD showed concomitant secondary OA.

Among 1113 knee arthroplasty cases (407 men, 706 women; age range, 38–93 years), 98 (9%) had CPPD. All had a pathologic diagnosis of OA (9% of total 1113 OA cases). The mean age of patients with knee CPPD also was significantly older than that of those without CPPD (72 versus 68, Student t test 2-tailed P < .001).

Of 78 shoulder joint cases (35 men, 43 women; age range, 38–85 years), 10 (13%) had CPPD on pathologic examination, 9 (90%) with a pathologic diagnosis of OA (13% of total 69 OA cases) and 1 (10%) with fracture (12% of total 8 fracture cases), but there was no significant difference in age between those with and those without CPPD (69 versus 64, Student t test 2-tailed P = .18). The sole case of humeral head AVN also did not show CPPD. The single humeral head fracture with CPPD did not show OA. These findings are summarized in Table 1.

Overall, the frequencies of pathologically confirmed CPPD in both knees (98 of 1113; 9%) and shoulders (10 of 78; 13%) were significantly higher than that in hips (61 of 2004; 3%) (χ² 2-tailed P < .001 for both knees versus hips and shoulders versus hips). However, there was no significant difference in frequency of CPPD between knee and shoulder cases (χ² 2-tailed P = .52). There were no significant differences in gender ratios among any of these patient groups.

Pathologic Features

Histologically, regardless of anatomic site, calcium deposits, when present, always involved the separately

Abbreviations: AVN, avascular necrosis; OA, osteoarthritis.

MATERIALS AND METHODS

Case Cohort

After obtaining approval from the institutional review board, we retrospectively reviewed consecutive total hip, knee, and shoulder arthroplasties (N = 3195) between January 1, 2017, and October 10, 2018, focusing on the presence of CPPD pathologically. Clinico-pathologic data including patient age (years), sex, site, underlying disease, and distribution of CPPD were correlated. Glass slides were reviewed for all cases.

Pathologic Examination

All specimens, accompanied by their specific surgical pathology requisition sheets containing pertinent clinical information and preoperative diagnoses, were received from our main or regional hospitals in a container of neutral buffered formalin, where they were further grossed and processed exclusively in our central anatomic pathology laboratory. All were grossly evaluated and sectioned using an electrical band saw. Femoral heads were initially oriented, grossly examined for any obvious lesions/abnormalities, and then bisected in the coronal plane. The anterior and posterior halves were additionally bisected, resulting in 4 quadrants. At least 1- to 2-mm sections were taken from the quadrant pieces, to include articular cartilage and, for example, any subchondral necrosis, fracture lines or defects, osteophytes, and/or eburnation, and submitted for decalcification, processing, and histologic evaluation, with the final number of sections and blocks also dependent upon the presence of other pertinent gross pathologic findings. If present, soft tissue/synovium/joint capsule also was sampled (focusing on abnormalities if noted), processed routinely without decalcification procedures, and evaluated histologically. A similar process is used for knee arthroplasty specimens, but sections through femoral condyles and tibial plateau generally occur in the sagittal/parasagittal plane. Femoral heads are handled similarly to femoral heads.

Clinicoradiologic Information

Clinical information including patient age (in years) and gender was correlated with the above data. To ensure accurate clinical preoperative diagnoses (not typographical or clerical errors), the operative report clinical diagnosis was also compared with the surgical pathology requisition clinical data for all cases. We then reviewed all preoperative radiology reports and their presumptive diagnoses that may have contributed to the preoperative clinical impression.

Statistical Analysis

Statistical comparison was performed using χ² analysis for categorical data and Student t test or analysis of variance for mean comparison, with a P-value probability threshold of < .05 considered statistically significant.
submitted joint capsules/synovium/tenosynovium when sampled (Figure, A and B), but only rarely involved the adjacent articular cartilage (5 [2 in hips, 3 in knees] of 169 cases with CPPD; 3.0%) (Figure, C and D). The crystalline material was composed of mostly uniform and small rhomboid to rectangular crystals, weakly polarizable, within a background of variably developed chondroid metaplasia, in the absence of a significant surrounding histiocytic giant cell reaction.

However, arthroplasty cases with a soft tissue block from submitted joint capsule/synovium represented 44.2% (1412) of all 3195 arthroplasty cases; more specifically, 46.0% (922) of 2004 femoral heads, 42.5% (473) of 1113 knees, and 21.8% (17) of 78 shoulders had a joint capsule/synovial tissue block. The calcium deposits were not documented (or seen) grossly per the pathology reports; as this was a retrospective review, the gross specimens were previously discarded.

Clinicoradiologic Correlation of Pathologically Confirmed CPPD-Positive Arthroplasty Cases

Among the 169 arthroplasty cases with CPPD confirmed pathologically, only 35 (21%) were detected/documente on preoperative radiologic evaluation; an additional 3 cases (1 hip, 2 knee) were detected via synovial fluid analysis. For radiologically detected cases, all but 1 were by plain film imaging; of these, chondrocalcinosis was reported in the same joint in 29 (30%) of the 98 knee arthroplasty cases with CPPD, but only 5 (8%) of the 61 hip and 1 (10%) of the 10 shoulder arthroplasties with CPPD. This fact that radiology reports more often detected and documented chondrocalcinosis in the knees versus the hips or shoulders was statistically significant ($\chi^2 P = .003$). Radiology reports less often (21 cases; 12%) documented chondrocalcinosis in other joints (most commonly knee and wrist) but not in the same pathologically examined joint where we confirmed CPPD. In a single case, CPPD was clinically suspected based on patient symptoms (eg, chronic multiple joint pain). All of these findings are summarized in greater detail in Table 2.

DISCUSSION

The diagnosis of CPPD most commonly refers to an idiopathic arthritis caused (or complicated) by CPP crystals, usually visibly recognized as chalky white deposits in arthritic joints and related soft tissues. Historically, CPPD
disease often has been referred to as pseudogout. This term appears to have originated from an earlier report of a disease regarding patients presenting with acute goutlike arthritis, whose synovial fluid showed crystals that were resistant to uricase digestion. During the same time period, Žitnani and Sit’Aja described a series of patients with chronic episodic inflammatory oligoarthritis, mostly of the knee, with radiologic findings of articular cartilage calcification following the contour of the epiphysis, designated chondrocalcinosis articularis. Patients with CPPD rarely present with tumorlike masses, which may be referred to as tophaceous pseudogout. Not surprisingly, the nomenclature and variety of terms used for CPPD has led to quite a bit of confusion. Ultimately, the designation CPPD disease was adopted to encompass the range of diseases (and designations) associated with primary CPP crystal deposition, including pseudogout and chondrocalcinosis.

Data on the prevalence of CPPD are highly variable and dependent on the methods (eg, radiographs, synovial fluid, joint resections) used and the population sampled. Community studies in the United Kingdom reported an approximately 7% prevalence of knee chondrocalcinosis, which compares with about 8.1% in the United States. A similar community study in Italy, including radiographs from both the knees and the pelvis, documented a slightly higher prevalence of 10.4% for chondrocalcinosis. When radiographs of the knees, pelvis, and hands were included in a separate evaluation, an estimated prevalence of 13.7% for chondrocalcinosis was suggested. Studies that analyzed the presence of CPP crystals in synovial fluid samples of patients undergoing total knee arthroplasty confirmed their presence in 30% to 53% of patients. Among the 12 patients in their small series, pseudogout was the preoperative diagnosis in only one patient, but all patients presented with local signs and symptoms characteristic of OA. On histologic examination, basophilic crystalline deposits were noted in or near the synovium, usually not associated with a histiocytic giant cell reaction. Sokoloff and Varma studied 55 knee (all with OA) and 177 hip (93 with fracture, 84 with OA) arthroplasty specimens and identified CPPD in 33% of knee joints but only 5% of hips (6% with OA and 4% with fracture). Fuerst et al analyzed articular cartilage from the medial femoral condyle of patients with knee OA and identified CPP crystals in 9 (18%) of 50 cartilage specimens. More recently, for 3200 femoral head specimens, Liow et al found 128 cases (4%) of CPPD, whereas Lin et al reported 4 cases (0.5%) of CPPD among 837 total knee resections but none among 456 hips. Additional arthroplasty studies involving pathologic evaluation have not found or documented any CPP deposits in hip or knee arthroplasty specimens.

Importantly, in none of the above studies were the specific clinical (demographic) characteristics, radiologic findings, or pathologic distribution of CPPD documented further or analyzed, especially among the more recent series. In our patients, CPPD was more often seen in the knees (9%) and shoulders (13%) compared with the hips (3%), and this finding was statistically significant. Regardless of anatomic site, calcium deposits, when present, always involved the separately submitted joint capsule/synovium and fibrocartilage but only rarely (3.0%) involved the adjacent articular cartilage concomitantly. Importantly, the percentage of arthroplasty cases with a soft tissue block from submitted joint capsule/synovium was 45.7% for all arthroplasty cases (46.0% of femoral heads, 42.5% of knees, and 21.8% of shoulders), suggesting that the true incidence of CPPD is likely underestimated because of undersampling. This finding may help explain some differences in prevalence between various studies. It also is possible that more meticulous soft tissue sampling, particularly focusing on menisci (in knee specimens), may have resulted in the true incidence of CPPD in our study being underestimated.

Regardless of anatomic site, the vast majority of CPPD cases in our series were not recognized preoperatively via radiographs. Although radiologic imaging remains a mainstay for detection of CPPD, studies have shown that conventional plain film radiography detects only about 40% of clinically important CPPD, and magnetic resonance imaging appears less sensitive than conventional radiographic imaging and histologic analysis. In terms of sites affected by CPPD, numerous reports have established that knees are by far the most commonly affected joint, followed by the wrists, hips, symphysis pubis, metacarpophalangeal, and acromioclavicular joints. In our series, all CPPD cases but one were analyzed solely by plain films. However, among the entire 169 arthroplasty

| Table 2. Clinicoradiologic Correlation of Pathologically Confirmed Calcium Pyrophosphate Dihydrate Deposition–Positive Arthroplasty Cases |
| Clinicoradiologic Correlation | Hip | Knee | Shoulder | Total |
|--------------------------------|-----|-----|---------|------|
| Detected on radiology, No. (%) |     |     |         |      |
| Yes; chondrocalcinosis at same site | 5 (8) | 29 (30) | 1 (10) | 35 (21) |
| No |     |     |         |      |
| Chondrocalcinosis detected elsewhere | 10 (16) | 8 (8) | 3 (30) | 21 (12) |
| Chondrocalcinosis not detected anywhere | 45 (74) | 58 (59) | 6 (60) | 109 (64) |
| Diagnosed by other means, No. (%) |     |     |         |      |
| Detected in synovial fluid | 1 (2) | 2 (2) | 0 | 3 (2) |
| Suspected based on symptoms | 0 | 1 (1) | 0 | 1 (0.5) |
| Total | 61 | 98 | 10 | 169 |
cases with CPPD detected pathologically, only 35 (21%) were documented in the preoperative radiology report. Chondrocalcinosis was reported in 29 (30%) of the 98 knee arthroplasties with pathologically confirmed CPPD, but only 5 (8%) of the 61 hip and 1 (10%) of the 10 shoulder arthroplasties with CPPD. This fact that radiology reports more often detected and documented chondrocalcinosis in the knees compared with the hips or shoulders was statistically significant ($\chi^2 P = .005$). Whether an inherent bias contributed to this discrepancy and/or it reflects deficiencies in the radiologic interpretation of calcifications in the hips compared with the knees is unclear.

The significant association between CPPD disease and age has been well established by numerous studies,\textsuperscript{7,9,24} with a reported 15% to 30% increased prevalence among patients older than 80 years compared with patients aged between 60 and 70 years.\textsuperscript{8,24} Results regarding gender predilection have been more mixed and less clear. One study suggested an absence of association with sex,\textsuperscript{9} whereas another found a significantly higher incidence of CPPD in women compared with men.\textsuperscript{8} In our series, the patients with hip (mean age, 73 years) and knee (mean age, 72 years) CPPD were significantly older than those without the disease (mean age, 66 and 68 years, respectively; $P < .001$). Nevertheless, CPPD was not exclusive to the elderly, as we also confirmed its presence in a minority of patients below 50 years of age (the youngest being 45 years). There was no significant association between gender and the presence or absence of CPPD.

The relationship between CPPD and OA is complex. Although multiple studies have reported a strong association between CPPD disease and OA,\textsuperscript{7,8,16,27,29} whether CPPD predisposes to OA remains controversial.\textsuperscript{2,6} In contrast, 2 cross-sectional studies reported significant association between OA and chondrocalcinosis whether or not the affected joints were the same or contralateral distant, but this association applied only for knee and wrist OA, and not for hip OA.\textsuperscript{30,31} In one of the few long-term studies with clinical follow-up, Reuge et al\textsuperscript{32} followed a cohort of 59 patients with idiopathic knee OA for 8 to 10 years and identified 15 (25%) who developed CPPD (detected by radiographs or synovial fluid analysis), and these patients were more likely to require surgery compared with those without CPPD. We found CPPD most commonly associated with OA in total hip, knee, and shoulder resections; however, we also found deposits of CPP in the joints of rare patients with hip fractures not associated with OA. All 3 examples of AVN of the femoral head with CPPD had concomitant OA.

In conclusion, among total joint resections, CPPD is at least 3 times as likely to occur in the knees and shoulders compared with the hips. Similar to prior reports, patients with CPPD in the knees and hips constitute a significantly older population than those without CPPD. Among hip and shoulder arthroplasties, CPPD is not exclusively associated with OA and also may be found in patients presenting with fracture and AVN (femoral head). Regardless of anatomic site, the vast majority of cases of pathologically confirmed CPPD are not detected preoperatively and/or radiographically, especially when the CPPD involves the hips and shoulders. To reliably establish the diagnosis of CPPD requires pathologic examination of the adjacent joint capsule/synovium, as it is only rarely seen in the articular cartilage. The frequency of CPPD is likely underestimated because of a slight majority of our cases lacked additional joint capsule/synovial tissue for histologic examination.

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