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Editorial

Can drugs trigger CPPD acute attacks?



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Calcium pyrophosphate deposition (CPPD) is a group of chronic conditions that are caused by the deposition of calcium pyrophosphate dihydrate (CPP) crystals in and around the joints. The terminology of CPPD is complex and recently the EULAR recommendations advise “CPPD” as the umbrella term for the conditions including acute CPP crystal arthritis (acute pseudogout), osteoarthritis with CPPD and chronic CPP crystal inflammatory arthritis while chondrocalcinosis simply indicates cartilage calcification [1].

The prevalence of CPPD is difficult to estimate. Chondrocalcinosis seems not uncommon, particularly in the elderly. A large UK community study examining radiography of 1727 people > 40 years found 117 (7%) of them had chondrocalcinosis and the prevalence of radiographic chondrocalcinosis is proportional to age, increasing from 3.7% in those aged 55–59 to 17.5% in those aged 80–84 [2]. In patients with osteoarthritis, the prevalence is significantly higher than controls [3]. For example, among people with osteoarthritis requiring total joint arthroplasty, up to 60% of patients have CPP crystals identified from their synovial fluid [4]. Interestingly, only half of them has radiographic chondrocalcinosis. Chronic recurrent oligoarthritis or polyarthritis mimicking osteoarthritis or rheumatoid arthritis is less common. While most patients with CPPD has an indolent disease course, acute attacks do occur which may be one of the most common monoarthritis in the elderly. However, it is still unclear what elicit acute attacks and why only part of CPPD patients suffer acute attacks.

The mechanisms of CPPD are summarized in Fig. 1. The central pathogenesis of CPPD is the dysregulation of inorganic pyrophosphate which results in the formation of rhomboid or parallelepipedic CPP crystals and deposition in the matrix of fibrocartilage and hyaline cartilage. Extracellular pyrophosphate primarily came from the degradation of adenosine triphosphate (ATP) by the enzyme ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP-1) [5] and intracellular inorganic pyrophosphate outflow by progressive ankylosis protein homolog (ANKH) transporter [6]. The extracellular pyrophosphate is degraded by tissue non-specific alkaline phosphatase (TNAP) with the cofactor of magnesium [7]. The shedding of CPP crystals can induce NLRP3 inflammasome formation and subsequent secretion of inflammatory cytokines

such as interleukin-1 β [8]. The cascade of inflammatory response including matrix metalloproteinases or prostaglandin E2 release in synovium [9] and neutrophil chemotaxis [10] results in intense inflammation and clinically evident acute attacks. Therefore, factors that increase the risk of acute attacks involve:

- alteration of the concentrations of calcium, inorganic phosphate, inorganic pyrophosphate and the solubility products of these ions;
- changes in inflammatory cytokine milieu and;
- mechanical or chemical forces that enhance CPP crystal shedding.

Currently accepted risk factors for CPPD as summarized in Table 1 seem compatible with known pathogenesis. Aging and osteoarthritis, for example, are found to enhance the expression of ENPP-1 and ANKH, increase the availability of extracellular pyrophosphate and increase CPP crystal deposition [11]. The occurrence of chondrocalcinosis is typical for Gitelman's syndrome, which is characterized by hypomagnesemia [12]. Apart from confirmed risk factors for CPPD acute attacks, there is also evidence suggesting the association between certain medications and acute attacks of CPPD (Table 2). Loop diuretic, bisphosphonate, hyaluronic acid and granulocyte colony-stimulating factor are found to associate with an increased risk of CPPD acute attacks among people with pre-existing CPPD. However, the associations are not consistent or are only supported by case reports.

Loop diuretics are linked to chondrocalcinosis and CPPD acute attacks because it inhibits magnesium reabsorption which results in hypomagnesemia. A nested case-control study using UK primary care database between 1986 to 2007 identified 795 cases of CPPD acute attacks. Loop diuretic use was associated with an odd ratio (OR) of 1.35 for acute attacks [13]. In contrast, another large study consisting of 25,157 US veterans of US showed that negative association (OR, 0.80) between loop diuretics and CPPD [3].

Since 1997, there are many case reports showing that bisphosphonates can trigger CPPD acute attacks [14–20]. In 2017, a case-control study in UK founded that 6.1% of patients with CPPD acute attacks received an oral bisphosphonate prescription within the 60-day period before the index date compared to 3.8% of matched controls (risk ratio, 1.33) [21]. Hypotheses for this association include sudden fall in serum calcium levels which promote shedding of CPP crystal, inflammatory cytokine (IL-6 and TNF α) elevation and structure similarities between bisphosphonate and pyrophosphate which may inhibit TNAP activity. However, the US

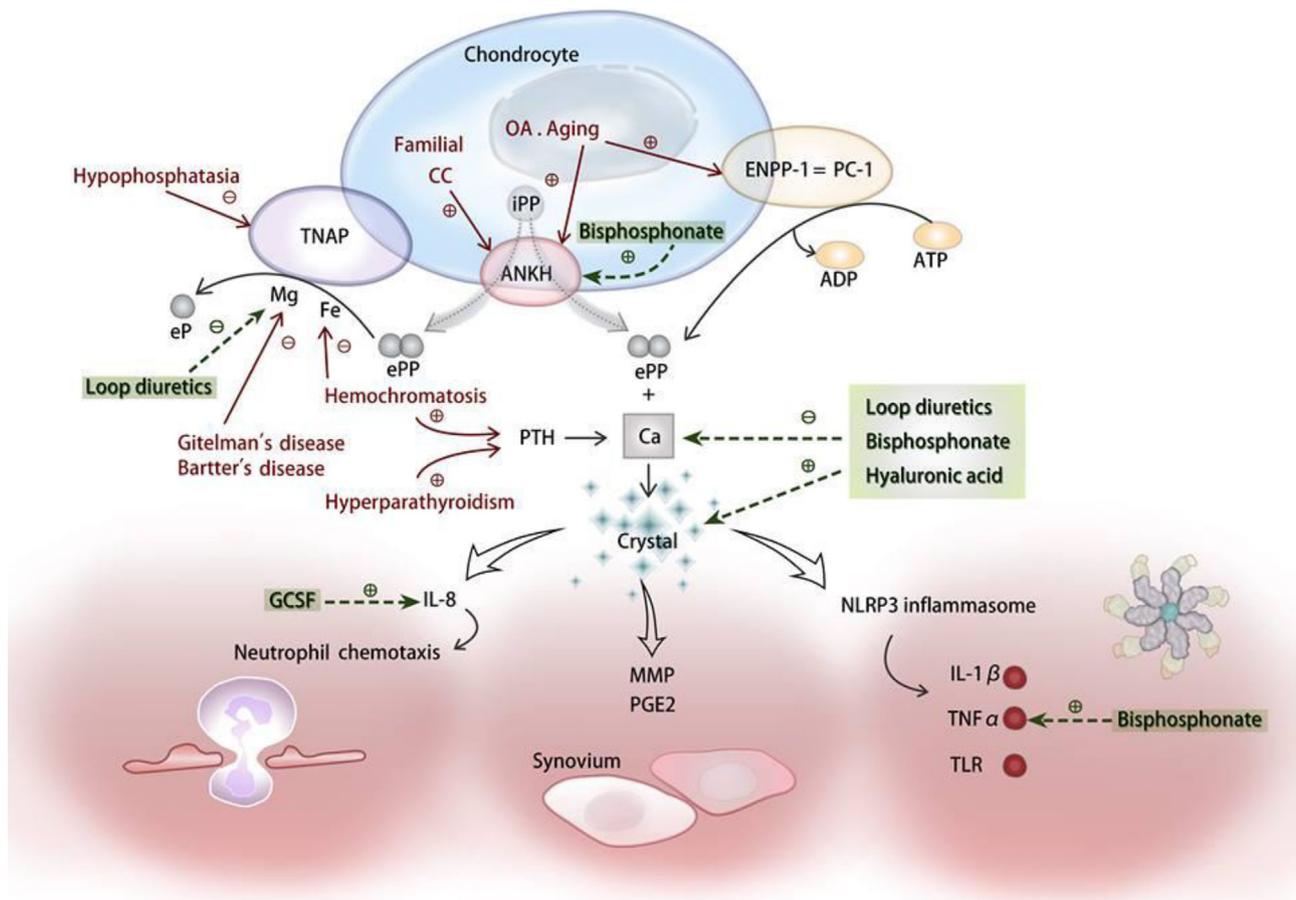


Fig. 1. Medications in calcium pyrophosphate deposition mechanism. ADP: adenosine diphosphate; ANKH: human homolog of the murine progressive ankylosis; ATP: adenosine triphosphate; Ca: calcium; ENPP-1: ectonucleotide pyrophosphatase/phosphodiesterase 1; eP: extracellular inorganic phosphate; ePP: extracellular inorganic pyrophosphate; Familial CC: familial chondrocalcinosis; IL: interleukin; iPP: intracellular pyrophosphate; MMP: matrix metalloproteinases; NLRP3: nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 or Nod-like receptor protein 3; OA: osteoarthritis; PC-1: plasma cell alloantigen 1; PGE2: prostaglandin E2; TNF: tumor necrosis factor; PTH: parathyroid hormone; TLR: toll-like receptor; TNAP: tissue non-specific alkaline phosphatase.

Table 1
The risk factors and treatment of calcium pyrophosphate deposition for consistency in terminology.

	Risk factor	Treatment
Asymptomatic chondrocalcinosis	Age	Observation
	Osteoarthritis Meniscectomy and joint injury Single nucleotide polymorphisms (SNPs) in ANKH gene Metabolic disease: hyperparathyroidism; hemochromatosis; hypomagnesemia; hypophosphatasia; chronic kidney disease stage 5 and Wilson's disease Low metacarpal bone mineral density	
Acute attack of CPPD	Hyperparathyroidism	Rest and ice pack
	Chronic kidney disease stage 5	Intra-articular and oral glucocorticoid, colchicine, nonsteroidal anti-inflammatory drug, interleukin-1 inhibitor
Chronic recurrent CPPD	Osteoarthritis Unknown	Hydroxychloroquine, methotrexate, interleukin-1 inhibitor

veterans study, which reported an OR of 0.85 for the association between bisphosphonate and CPPD acute attacks [3].

Proton pump inhibitor has been linked to hypomagnesemia[22] which is an established risk factor for CPPD. This is mainly due to gastric acidity's role in the absorption of calcium and magnesium. However, the US veteran study found a negative association between proton pump inhibitor and CPPD, with an OR of 0.58 [3]. Interestingly this study found a negative association

between the aforementioned medications (loop diuretics, bisphosphonate and proton pump inhibitors) and CPPD. This study used a cross-sectional design based on electronic health databases. The established association should be confirmed using a more robust study design such as a cohort study.

There are several case reports demonstrated that hyaluronic acid injection in osteoarthritis would cause CPPD acute attacks [23–26]. Granulocyte colony-stimulating factor exposure has also

Table 2
Conflicting result of drugs trigger CPPD acute attacks.

Authors	Study design	Main findings	Possible mechanistic explanation
<i>Loop diuretic</i>			
Rho et al. (2012) [13]	Cross-sectional study using the UK primary care data (the Health Improvement Network) with 795 cases of pseudogout	Positive association (OR 1.35; 95% CI 1.09–1.67)	Increase urinary magnesium and calcium loss
Kleiber Balderrama et al. (2017) [3]	Cross-sectional study using the US Veterans Affairs population with 25,157 cases of CPPD.	Negative association (OR 0.8, 95% CI 0.76–0.84)	Magnesium level is similar in sporadic CPPD and matched people
<i>Bisphosphonate (zoledronic acid, pamidronate, alendronate, etidronate, neridronate)</i>			
Couture et al. (2017), [15] Young et al. (2005), [16] Watanabe et al. (2006), [14] Wendling et al. (2008), [18] Carda et al. (2010), [17] Malnick et al. (1997), [19] Gallacher et al. (1991) [20]	Case reports	Acute CPPD attack in 2 patients exposed to intravenous zoledronic acid, 2 to oral etidronate, 1 to oral alendronate, 2 to intravenous pamidronate and 1 to intravenous neridronate.	Fall in tissue calcium levels IL-6 and TNF elevation Inhibition of TNAP activity
Roddy et al. (2017) [21]	Matched case-control study using the UK primary care data (Clinical Practice Research Data-link) with 2011 cases of incident pseudogout.	Positive association (Adjusted IRR 1.33, 95% CI 1.05–1.69)	
Kleiber Balderrama et al. (2017) [3]	Cross-sectional study using Veterans Affairs population with 25,157 CPPD cases.	Negative association (OR 0.85, 95% CI 0.78–0.93)	
<i>Proton pump inhibitors</i>			
Kleiber Balderrama et al. (2017) [3]	Cross-sectional study using Veterans Affairs population with 25,157 CPPD cases.	Negative association (OR, 0.58; 95% CI 0.55–0.60)	Fall in tissue calcium levels IL-6 and TNF elevation Inhibition of TNAP activity
<i>Hyaluronic acid</i>			
Ali et al. (1999), [26] Dosla et al. (1999), [23] Mailliefert (1999), [24] Kroesen (2000) [25]	Case report	4 cases of patients developed single or recurrent CPPD acute attacks 1–7 days after exposure to intra-articular hyaluronic acid injection.	PH alteration High phosphate level may induce local drop of calcium level
<i>Granulocyte colony-stimulating factor</i>			
Yamamoto et al. (1999), [27] Ames et al. (2007) [28]	Case report	2 cases of patients developed acute CPPD attacks after 4/5 days of G-CSF injections.	Increase phagocytosis of CPP crystals IL-6 and IL-8 elevation

been reported to trigger acute CPPD attacks [27,28]. However, no formal controlled study has been conducted to support these associations.

Therefore, existing evidence is conflicting for the association between loop diuretics and bisphosphonate and CPPD acute attacks. For hyaluronic acid injection or granulocyte colony-stimulating factor exposure, the current evidence is too scarce to conclude. Further study is warranted to confirm these associations. In the meantime, physicians should be aware of the risk of CPPD acute attacks and be cautious when prescribing a loop diuretics and bisphosphonate to people with advanced age, chondrocalcinosis, metabolic disturbance, electrolyte imbalance and renal function impairment.

Disclosure of interest

The authors declare that they have no competing interest.

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