Tumoral calcinosis: a rare and disabling bone disorder

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ABSTRACT

Familial tumoral calcinosis (TC) is an extremely rare disease characterized by multilobulated calcific masses most commonly occurring within the periarticular soft regions of large joints. Two forms of TC have been reported according to the literature. Normophosphatemic TC (NTC) is a genetically determined disorder caused by mutations in the sterile alpha motif domain containing 9 gene (*SAMD9*). Instead, hyperphosphatemic TC (HTC) is caused by variations in *FGF23* (the gene encoding fibroblast growth factor 23, a phosphaturic protein and important hormone regulator of phosphate homeostasis), in *GALNT3* (the gene encoding N-acetylgalactosaminyltransferase 3, which is responsible for *FGF23* O-glycosylation serving to protect intact *FGF23* from proteolytic processing), or in α-*Klotho* (a co-receptor for *FGF23* whose alteration leads to *FGF23* deficiency or resistance and consequently hyperphosphatemia and ectopic calcification). A variety of treatment approaches have been attempted to manage blood phosphate levels, reduce pain and inflammation, and treat HTC-associated calcifications and their complications. Unfortunately, efficacy data are limited to clinical case reports and small cohorts of patients, and no clearly effective treatment approaches have been identified so far. This concise review aims to provide a brief overview of current understanding of the etiopathogenesis, diagnostic modalities, and treatment options for HTC, and to discuss the currently available experimental models for studying the biological mechanisms underlying TC.

KEYWORDS

Tumoral calcinosis, ectopic calcifications, rare bone disorder.

Introduction

Familial tumoral calcinosis (TC) refers to a rare and heterogenous group of disorders characterized by deposition of ectopic calcified masses in different periarticular regions due to alterations in fibroblast growth factor 23 (FGF23)-mediated phosphate regulation [1]. Calcifications usually occur during the first three decades of life, even though the condition has also been documented as early as six weeks of age [2]. Typically, calcified nodules appear adjacent to large joints, including hips, shoulders, and elbows. Although initially asymptomatic, they progressively increase in size, limiting the individual's range of movement [3]. The first clinical description of TC dates back to the end of the 19th century when Giard and Duret first documented its distinctive features under the name of "endothelioma calcifié" [3]. The term TC was coined by Inclan *et al*. in 1943, who were also the first to discriminate this disorder from other acquired conditions, later identified as dystrophic calcinosis and metastatic calcinosis [3]. In particular, when cutaneous calcinosis is associated with connective tissue damage due to a systemic disease (i.e., systemic sclerosis, dermatomyositis, mixed connective tissue disease, or systemic lupus erythematosus), it is termed dystrophic calcinosis, whereas when it is caused by impaired calcium or phosphate metabolism (e.g., chronic renal failure), it is known as metastatic calcinosis [4,5]. In 1996, Smack *et al*. formally distinguished between hyperphosphatemic TC (HTC) and normophosphatemic TC (NTC), paving the way for the identification of the genetic basis of TC [6].

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Since the clinical and metabolic features of HTC and NTC are very similar to those of metastatic calcinosis and dystrophic calcinosis, respectively, elucidation of the molecular mechanisms underlying TC could shed light on the pathogenesis of these two forms of TC.

Metabolism and role of FGF23

FGF23 is a 32-kDa protein consisting of 251 amino acids primarily secreted by osteocytes, osteoblasts in bone, and erythroid precursors in bone marrow, which play a crucial role in phosphate regulation [7-9]. Intact FGF23 (iFGF23) is required to produce the effects of this phosphaturic hormone on calcitriol synthesis and kidney phosphate reabsorption [10]. FGF23 is initially transcribed and translated as an inactive 251-amino acid peptide that, following cleavage of the first 24 amino acids, termed the signal peptide, gives rise to iFGF23 [11], the biologically active form. It then undergoes a specific O-glycosylation at Thr178 by the enzyme N-acetylgalactosaminyltransferase 3 (GalNAcT3, encoded by *GALNT3*), which inhibits the action

of the proprotein convertase furin, thereby promoting secretion of iFGF23 [12]. On the other hand, phosphorylation at Ser180 by the Golgi kinase FAM20C inhibits GalNAc-mediated O-glycosylation, promoting cleavage of FGF23 into inactive C- and N- terminal fragments [13]. Once produced, FGF23 functions directly in the proximal tubule of the kidney by binding with FGF receptor 1 (FGFR1) and its co-receptor α-Klotho, decreasing expression of the type II sodium-phosphate cotransporters NPT2a and NPT2c, thereby leading to phosphaturia [14]. Moreover, FGF23 also binds to the FGFR1 c-splicing form (FGFR1c) in the parathyroid glands, resulting in a reduction of parathyroid hormone gene (*PTH*) expression and PTH secretion through activation of the MAP kinase cascade [15]. In addition, FGF23 stimulates 25-vitamin D-24 hydroxylase and inhibits 1α-hydroxylase, resulting in decreased levels of the biologically active form of vitamin D [14]. Collectively, FGF23 controls the homeostasis of both vitamin D and phosphate, thus decreasing blood levels of phosphate.

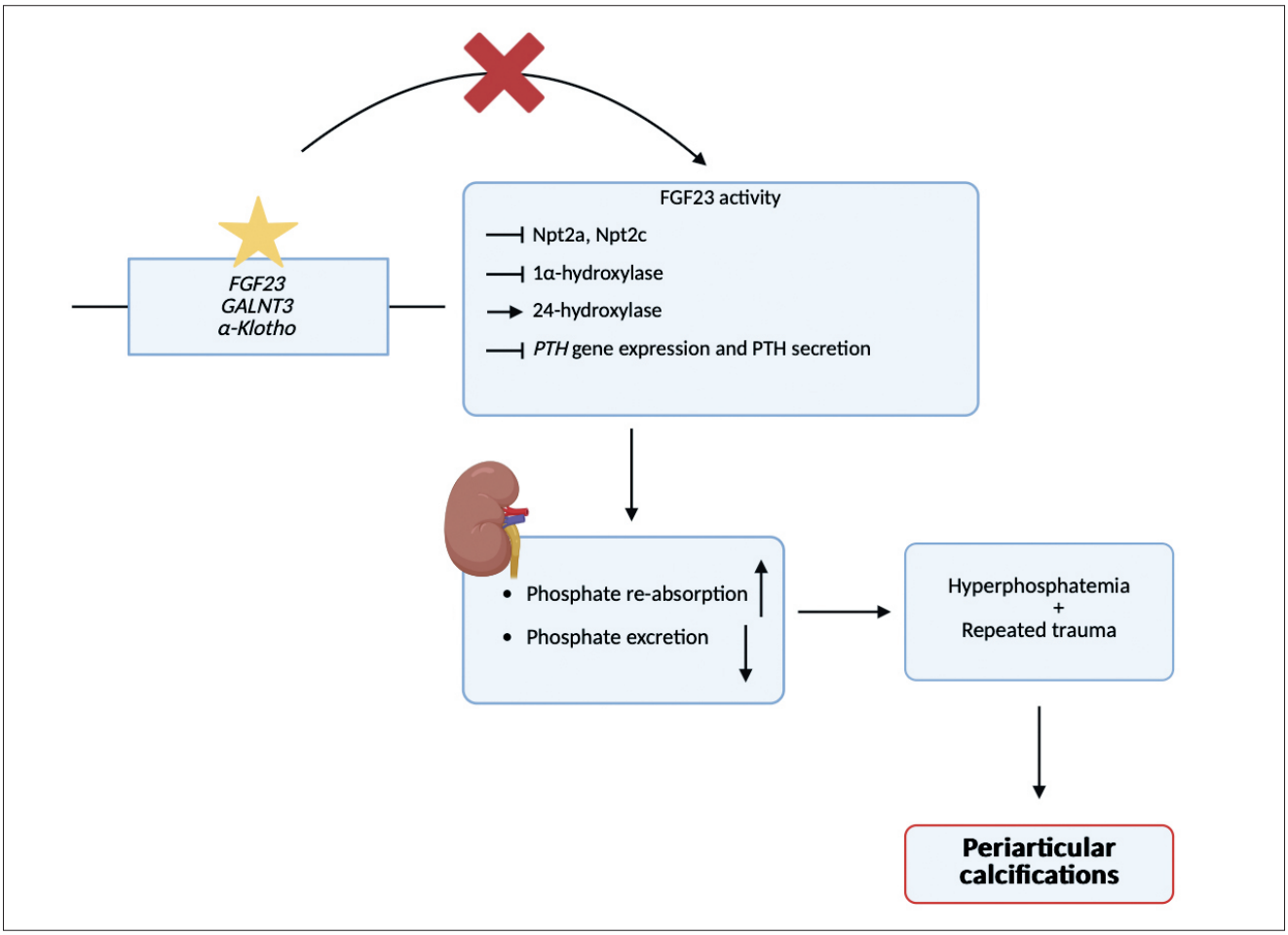
Pathogenesis, diagnosis and treatment

Two TC variants have been described, namely (I) HTC, also referred to as hyperostosis/hyperphosphatemia syndrome, in which blood phosphorus levels are elevated (normal range in adults: 2.5-4.5 mg/dL) and calcium levels are normal, and (II) NTC, in which the phosphate and calcium levels are adequate [3,16]. This latter variant is caused by loss-of-function mutations in the sterile alpha motif domain containing 9 gene (*SAMD9*), which encodes a TNF-alpha responsive protein with a tumour suppressor and anti-inflammatory function. The hyperphosphatemic variant is instead caused by recessive mutations in *FGF23*, *GALNT3* and α-*Klotho*, which lead to a deficiency of or resistance to the phosphaturic hormone FGF23 [1,17,18].

The etiopathogenesis of the HTC-associated ectopic calcification lesions is likely linked to repeated trauma in the most vulnerable periarticular soft tissue regions, which results in microhaemorrhages and thereby initiates a foamy histiocytic response involving macrophages with bursae forming activity [3,14]. Finally, calcified debris fills the cystic loculi leading to bone formation with arrest of the neobursae formation and loss of collagenolytic activity, resulting in fibrosis and development of the lesions typical of TC [19] (Figure 1).

Despite TC being an extremely rare disease with fewer than 100 genetically confirmed cases described in the literature, a spectrum of its clinical manifestations has emerged based on currently available data [20]. TC patients usually exhibit solitary or multiple heterogenous calcified masses related to the joints, pain, and joint movement impairment [21,22]. In addition, they may present with recurring bone pain, termed hyperosto-

Figure 1 Schematic diagram showing the pathogenesis of hyperphosphatemic familial tumoral calcinosis (HTC).



sis, particularly involving the tibias, even though other sites have been described, such as ulnas, radii and metacarpals [23]. In view of this, TC diagnosis is primarily based on imaging tests (i.e., radiography, magnetic resonance, computed tomography scintigraphy using phosphate-radiolabelled agents, and ultrasonography) to detect the distinctive manifestations around the periarticular regions, and evaluate their extent so as to be able to monitor therapeutic response and determine the activity of the TC-associated lesions [3,24].

Dental involvement is another key feature of HTC; partial obliteration of dental pulp and shortening of roots have been noted in several case reports [25]. In this regard, dental abnormalities are commonly the first reported manifestations of HTC before the development of calcifications. HTC patients have a distinctive thistle-shaped root with gross enlargement of the coronal third and an acutely tapering apical third of the root canal. Awareness of these features among dentists is important, to allow treatment measures to be undertaken [26-28]. Calcification of the eyelids, conjunctiva and cornea, as well as in the elastin-rich membrane between the choroid and retina, causing eye itching and discomfort, has been also described in HTC [29,30]. Other manifestations due to off-target effects of FGF23 have been described in HTC patients, including less prevalent complications affecting the gastrointestinal, cardiovascular, immune, and central nervous systems [14].

Because of the rarity of the different forms of TC, data on managing these very debilitating conditions are currently scarce. Furthermore, until recently, there were no studies shedding light on the distinction between HTC and NTC. Emerging evidence shows that these conditions, while similar in phenotype, arise from two distinct pathophysiological defects, as described above. It thus stands to reason that anti-inflammatory strategies are likely to benefit NTC patients, whereas HTC treatment, to be effective, should target the underlying metabolic abnormalities. Because of the pathogenic variants in *FGF23* and *GALNT3* that lead to reduced FGF23 activity, hormone replacement therapy with FGF23 would be the first choice to manage most of the causes of HTC. Pending routine use of this gene therapy, recent years have seen various approaches used to manage blood phosphate levels, to counteract inflammation and pain, and to address calcific lesions and their complications, including phosphate binders, anti-inflammatory and anti-mineralization therapies, as well as surgery and physiotherapy to restore mobility of the affected limb [31-34]. A diet low in phosphate is advised for HTC patients, although there is scarce evidence to suggest that this is sufficient on its own [35]. In an effort to diminish the calcium phosphate (CaP) product, drugs that hinder intestinal absorption of nutritional phosphate have been used in HTC patients, such as aluminium hydroxide, sevelamer and lanthanum [14]. Since HTC is associated with high levels of the biologically active form of vitamin D_3 [14,20,36], vitamin D-based therapies should never be given to patients with HTC, even in the presence of a hypovitaminosis D condition, and it is also important to avoid the use of calcium salts, as they may promote precipitation of CaP in the form of hydroxyapatite. Most HTC subjects have been treated with acetazolamide and probenecid to achieve increased phosphate excretion [22]. Acetazolamide is a carbonic anhydrase inhibitor that induces proximal tubular acidosis by blocking reabsorption of bicarbonate in the proximal tubule. Since this could potentially cause bicarbonate levels to exceed tolerable limits (> 20mmol/L), bicarbonate serum concentration should be measured repeatedly in HTC patients to avoid complications. Probenecid, instead, is an agent that stimulates uric acid excretion and promotes renal phosphate excretion. Given the ability of this drug to boost the half-life of many antibiotics (i.e. penicillin, trimethoprim-sulfamethoxazole, cephalosporins), probenecid should be used with caution when co-administered with these medications as it may result in antibiotic toxicity. Given the risks and high rate of recurrence, surgery is often avoided, being reserved for subjects with severe lesions (impairing daily living activities), chronic drainage, and infections [21,37]. Patients with significant inflammation, often manifested by erythematous, warm lesions, fever and increased C-reactive protein, may benefit from anti-inflammatory therapies [38,39]. Improvement of symptomatic hyperostosis has been reported with non-steroidal anti-inflammatory drugs and glucocorticoids. Moreover, the use of anakinra, a recombinant interleukin 1 (IL-1) receptor antagonist, and canakinumab, a monoclonal anti-IL-1β antibody, was found to ameliorate pain, inflammation and quality of life in a small cohort of patients [40]. Unfortunately, efficacy data are generally limited to clinical case reports and studies with small samples. Considering also the absence of longitudinal studies and the low patient compliance with medications, treatment safety and efficacy data are quite difficult to interpret. In this context, attempts have been made to treat HTC patients with other therapies, such as calcitonin, bisphosphonates, TNFα inhibitors and calcium-channel blockers, although many failed to provide substantial relief [14]. Recently, a mouse model of chronic kidney disease was used to investigate whether an oral inhibitor of the renal sodium-phosphate Npt2a co-transporter might increase phosphate excretion, reducing phosphatemia [41]. Further investigations are still ongoing to understand whether this class of drugs may be effective for HTC treatment.

Experimental models of HTC

Although several murine models have been developed to produce the biochemical abnormalities characteristic of TC, research efforts to reproduce in animals what happens in humans are still ongoing. As reported by Ichikawa *et al*. [42], *Galnt3*-deficient mice showed marked hyperphosphatemia, despite higher levels of phosphate being present in the bone. In addition, this mouse model showed altered calcitriol levels, elevated circulating C-terminal FGF23, and low alkaline phosphatase activity. Despite the altered biochemical profile, no calcific lesions were noted in the experimental mice fed a normal diet, whereas calcifications were observed in half of those receiving high dietary phosphate [43]. Another model mouse of HTC was generated by N-ethyl-N-nitrosourea mutagenesis. These mice, too, exhibited hyperphosphatemia with reduced iFGF23 levels, elevated calcitriol levels, and the presence of periarticular calcifications [44].

In addition to murine models, *in vitro* models have been de-

veloped to study the biological mechanisms underlying TC. In a study by Shalhoub *et al*. [45], carried out on murine MC3T3.E1 osteoblasts, the FGF23/αKlotho axis modulated the expression of genes related to osteoblast differentiation and mineralization, presumably through FGFR1 signalling. In a previous study by Masi *et al*. [39], the authors established a primary cell line from subcutaneous adipose tissue of a TC patient affected by a novel mutation in the *GALNT3* gene. They discovered that this cell model had an increased ability to form hydroxyapatite crystals earlier and in greater quantities compared with cells obtained from healthy subjects. In a subsequent study, we established the first stem cell line obtained directly from the primary cell line described Masi *et al*., with the ability to grow in the absence of adhesion and under stress conditions, which could be helpful in clarifying the pathophysiology and the molecular mechanisms underlying TC pathogenesis and recurrence (article under peer review). Overall, research in this area is still in its infancy and more studies are needed to offer new insights into TC aetiopathogenesis and to identify novel targets for tailoring new modes of treatment for TC.

Conclusions

The study of HTC has significantly expanded our comprehension of phosphate homeostasis and led to new insights into the FGF23 signalling pathway. HTC can be the result of dysregulation of multiple signalling pathways leading to FGF23 deficiency and/or resistance, thereby resulting in hyperphosphatemia and ectopic calcifications. The development of clinical management approaches has lagged behind recent advances in understanding of the pathophysiology of HTC. Additional studies are therefore needed to uncover the TC-associated cellular and molecular mechanisms and thus pave the way for the design of innovative diagnostic and therapeutic approaches for this extremely rare bone disorder.

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