

ACTA ORTHOPAEDICA ET TRAUMATOLOGICA HELLENICA

BASIC SCIENCE

- Extra-skeletal calcifications. An overview of soft tissue calcifications and ossifications

ORIGINAL ARTICLE

- The combined intrarticular/intravenous administration of tranexamic acid in cemented total knee arthroplasty

REVIEW ARTICLE

- Slipped Capital Femoral Epiphysis:
Surgical Techniques, Complications, Special Topics

CASE REPORT

- Isolated hamate dislocation with simultaneous carpometacarpal subluxation. A case report



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“Acta Orthopaedica Et Traumatologica” is the official journal of the Hellenic Association of Orthopaedic Surgery and Traumatology, first published in 1948. This revived edition of Acta Orthopaedica Et Traumatologica, published in English, aspires to promote scientific knowledge in Orthopaedics and Traumatology worldwide. It is a peer-reviewed Journal, aiming at raising the profile of current evidence-based Orthopaedic practice and at improving the scientific multidisciplinary dialogue. Acta Orthopaedica Et Traumatologica Hellenica presents clinically pertinent, original research and timely review articles. It is open to International authors and readers and offers a compact forum of communication to Orthopaedic Surgeons and related science specialists.

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Papaioannou NA, Triantafyllopoulos IK, Khaldi L, et al. Effect of calcitonin in early and late stages of experimentally induced osteoarthritis. A histomorphometric study. *Osteoarthritis Cartilage* 2007; 15(4): 386-95.

■ Book chapters:

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Extra-skeletal calcifications

An overview of soft tissue calcifications and ossifications

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ABSTRACT

Extraskeletal calcifications is a common radiographic finding. The classification of the deposition of calcium and phosphorous salts in the soft tissues includes metastatic calcification, dystrophic calcification and calcinosis. **Metastatic calcification** develops when the calcium-phosphorous levels are elevated and implicate normal tissues. Conditions associated with metastatic calcifications are hyperparathyroidism, malignancies, hypervitaminosis D and milk-alkali syndrome. **Dystrophic calcification** is the calcification occurring in degenerated or necrotic tissues without imbalance in the metabolism of calcium and phosphorous. It is associated with multiple clinical conditions such as venous insufficiency, granulomatous infection, cysticercosis, neoplasms (primary bone forming tumors: osteosarcoma, other sarcomas especially synovial sarcoma), tumor necrosis, scleroderma, dermatomyositis and CREST syndrome, as well as with trauma (heterotopic ossification and injection granuloma). Calcinosis, also known as dystrophic calcification, is a distinct type of extra-skeletal calcification and it is usually not associated with calcium and phosphorus abnormalities. **Calcinosis** reveals most often in subcutaneous tissues, skin, and related connective tissues. It has been described in inflammatory connective-tissue diseases, including SLE, scleroderma and dermatomyositis. Other associated disorders include: calcinosis universalis, calcinosis circumscripta and tumoral calcinosis.

KEY WORDS: soft tissue; calcium deposition; calcification; ossification

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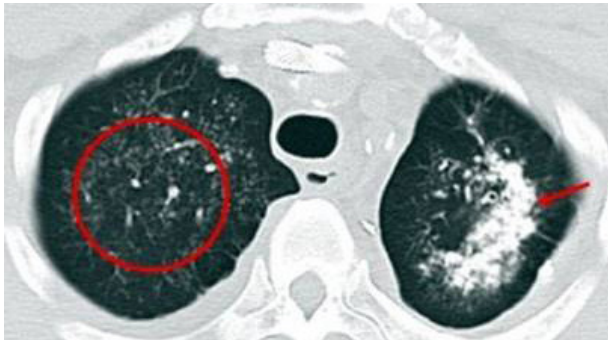


Fig.1 Metastatic calcification of the lung secondary to chronic renal disease and hyperparathyroidism



Fig.2 Coronary artery calcifications and calcifications of the descending thoracic aorta in a patient with chronic kidney disease

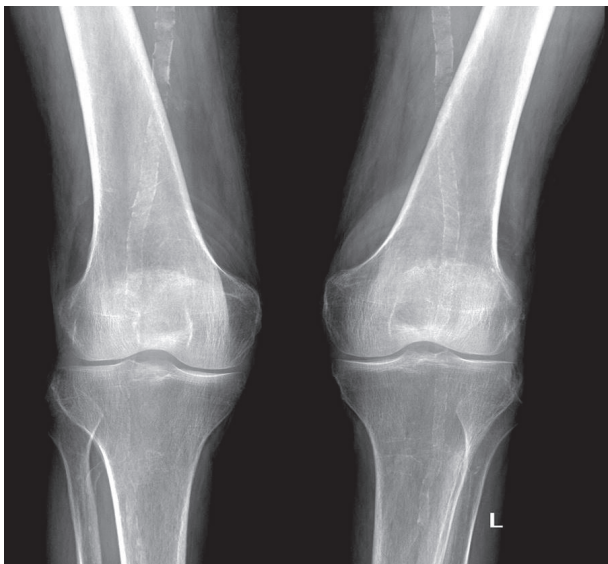


Fig.3 Patient with end stage renal failure (ESRF). There is extensive metastatic calcification involving the femoral, popliteal and tibial arteries

Introduction

Extra-skeletal deposition of calcium and phosphate has been associated with a considerable number and variety of disorders. This extra-skeletal deposition sometimes takes the form of amorphous calcium phosphate or hydroxyapatite crystals and sometimes bone tissue formation is noted. The classification of the deposition of calcium and phosphorous salts in the soft tissues includes metastatic calcification, dystrophic calcification and calcinosis [1-3].

There are three underlying mechanisms in relation to the pathogenesis of the ectopic mineralization on these disorders [4]. One mechanism that can cause metastatic calcification is a supra-normal "calcium/phosphate solubility product" in extracellular fluid. The second mechanism, in spite of normal serum levels of calcium and phosphate, mineral may be deposited as dystrophic calcification into metabolically damaged or dead tissue. Third, heterotopic ossification develops in a few disorders, for which the pathophysiology is unknown. Probably, according to some theories, a local tissue injury causes a cellular response which releases chemical mediators that stimulate excessive bone proliferation. This is most frequently seen in musculoskeletal trauma. This review describes the different categories of extra-skeletal calcification with reference to the pathogenesis, the clinical presentation, the laboratory and radiographic findings as well as the treatment the prognosis.

Distinction between Ossification and Calcification

Ossification is the process of bone tissue formation. In any region where there are fibroblasts, superfluity of calcium and sufficient blood-supply bone may form. Ossification forms a new bone. There is a surrounding shell of dense cortical bone, which surrounds a central medullary space [5].

Calcification is the deposition of calcium salts in a body tissue. The term pathological calcification refers to the abnormal deposits of calcium salts in any tissue except teeth and bones. Soft tissue calcification arise in the appendicular skeleton in different compartments which are the subcutaneous, neurovascular, fascial, muscular, and periarticular compartment. In the axial skeleton (calcification is found at spine) the soft tissue compartments such as the anterior longitudinal ligament, posterior longitudinal ligament, intervertebral disk, in-

terspinous and supraspinous ligaments, and paravertebral soft tissues [2]. There are two distinct types of pathological calcification: Metastatic calcification and dystrophic calcification.

A. Metastatic calcification

Metastatic calcification (MC) refers to deposition of amorphous calcium phosphate and calcium hydroxyapatite crystals in tissues and it is often associated with metabolic disorders, secondary to an increased serum calcium-phosphorous product. MC usually occurs with a calcium phosphorus product greater than 70 mg/dL [6]. Microscopic calcification is common in lungs, kidneys, stomach and calcium salts and may also be deposited diffusely in the soft tissues, blood vessels, or in intra or para-articular locations.

Epidemiology-Etiology

MC is a frequent complication encountered in patients undergoing maintenance dialysis [7]. Entities that lead to MC due to hypercalcemia are primary hyperparathyroidism, Milk alkali syndrome, Vitamin D intoxication. There are other causes of hypercalcemia including sarcoidosis, Paget's disease, widespread malignancy and multiple myeloma which may cause similar soft tissue calcification, but the hypercalcemia usually is corrected or the cause proves fatal prior to radiographic detection of calcification. Also, secondary hyperparathyroidism and tumoral calcinosis are causes that lead to metastatic calcification due to hyperphosphatemia.

Radiologic Findings

MC from any cause may be "tumoral" or "diffuse" as well as intra- or para-articular. The location and morphologic appearance of MC represent nonspecific responses to the increased serum calcium-phosphorous product [8]. In patients with primary hyperparathyroidism intra-articular deposition of calcium pyrophosphate is not uncommon and crystals may be deposited in hyaline or fibrocartilage. In Milk Alkali Syndrome deposits of calcium salts can be diffuse, amorphous and may be seen particularly in the subcutaneous and para-articular areas. The calcium deposits may have variable size and can cause erosion in normal bone. Calcification may involve the kid-

neys, lungs, and blood vessels (**Fig.1, 2, 3**). Calcification in the extremities is commonly seen in patients with secondary hyperparathyroidism with renal osteodystrophy than in those with primary hyperparathyroidism. Particularly among dialysed patients diffuse tumor-like masses in the soft tissues, especially in para-articular locations, are frequently seen. With the correction of the metabolic abnormality these diffuse metastatic soft tissue calcifications may recede.

Treatment

Early recognition and prompt initiation of treatment is vital. The best treatment of MC is prevention with maintaining normal levels of calcium and phosphate. The decrease dietary calcium intake may be also helpful. In case of acute renal failure reported therapeutic strategies for the treatment and prevention of MC include: increasing dialysis dose, lowering serum calcium phosphorous and Ca×P solubility products, and avoiding calcium-based Pi binders and vitamin D analogs. Also intravenously administered sodium thiosulfate raises the solubility of calcium deposits [9]. In the treatment of both nephrolithiasis and tumoral calcinosis sodium thiosulfate is shown to be successful. It has antioxidant effects on endothelial cells, but its exact mechanism of effect is unclear.

B. Dystrophic Calcification

The term dystrophic soft tissue calcification enclose a broad spectrum of pathologies that cause soft tissue calcification. Essentially is the deposition of calcium salts in necrotic or degenerated tissues and generally is irreversible. The amorphous calcification that results may be small or large. In some cases, ossification may occur - this is characterized by cortical formation and a central medullary cavity. Almost every calcification that one sees in the soft tissues in actual radiographic practice is due to dystrophic calcification. They have a high prevalence of 95%-98% of all soft tissue calcification [6]. Usually the calcium metabolism and the calcium serum levels are normal.

For the differential diagnosis of dystrophic calcifications it is useful to memorize the VINDATE (Vascular, Infectious, Neoplastic, drud, Autoimmune, traumatic, and Extraneous etiologies diseases) classification: [2].

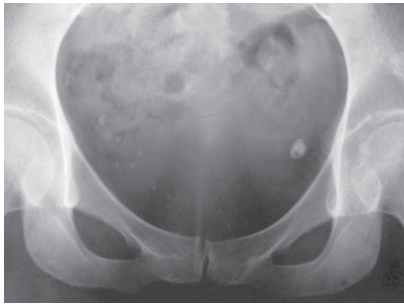


Fig.4 Dystrophic Calcification – Vascular. Patient with multiple bilateral phleboliths in the pelvic veins with characteristic central lucency

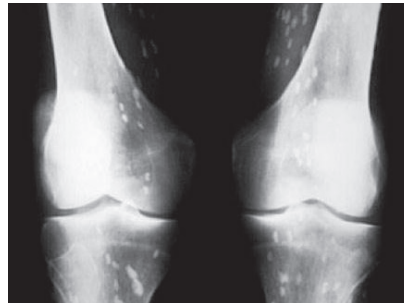


Fig.5 Dystrophic Calcification – Infection. Patient with multiple «rice-grain» calcifications in muscles about knees due to cysticercosis. The calcifications are oriented along the direction of the muscle fibers

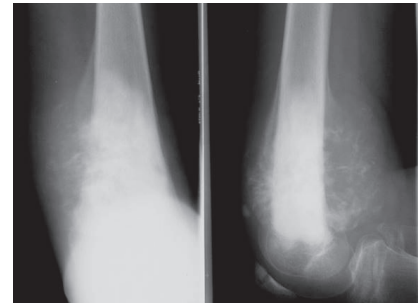


Fig.6 Dystrophic calcifications – Neoplasm. Osteosarcoma may occasionally metastasize to soft tissue. This is uncommon, and can mimic heterotopic ossification

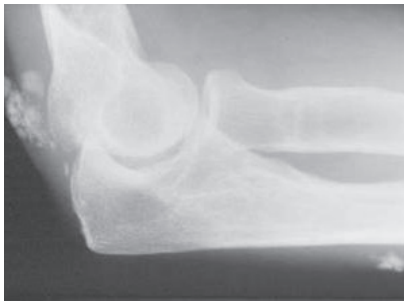


Fig.7 Dystrophic Calcification – Drugs. Hypervitaminosis D - Calcification over the elbow



Fig.8 Dystrophic Calcification- Trauma. Patient with Achilles tendon calcification due to recurrent trauma and tendinitis

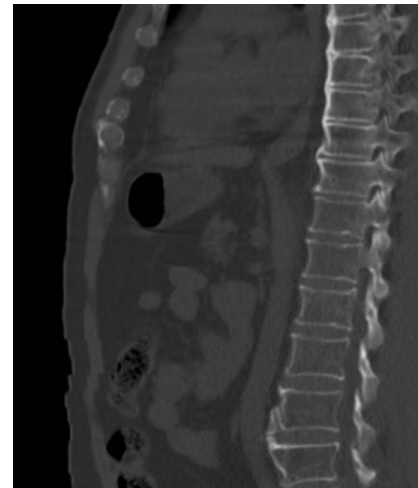


Fig.9 DISH. Ossification of the anterior longitudinal ligament in thoracic spine

■ Vascular

- Venous insufficiency as in phleboliths. Phleboliths are focal calcifications, often with radiolucent centers which is a helpful sign to distinguish them from urolithiasis. This appearance is attributed to calcification peripherally within the vessel, and is frequently seen on abdominal radiographs (66% of phleboliths) (Fig.4).

■ Infection

- Granulomatous infection

- Parasitic infestation

- Cysticercosis (the classic findings are multiple elongated foci of calcification just about the shape and size of grains of rice. These “rice grain” calcifications are usually oriented along the direction of the muscle fibers.) (Fig.5).
- Dracunculiasis (forms small crescentic calcifications)
- Armillifer armillatus tropical disease

■ Neoplasm

- Primary bone-forming tumors: osteosarcoma (Fig. 6)

- Other sarcomas: specially synovial sarcoma
- Osteoma
- Tumor necrosis

■ Drugs

- Vitamin D hypervitaminosis (Fig. 7)
- Milk-alkali Syndrome

■ Autoimmune

- Dermatomyositis
- Scleroderma
- Crest Syndrome: calcinosis cutis (usually under the skin of the hands or wrists), Raynaud's phenomenon, esophageal disorders, sclerodactyly, telangiectasia.)

■ Trauma

- Heterotopic ossification (Fig. 8)
- Injection granuloma

■ Extra

- DISH (Fig. 9)
- Ankylosing spondylitis

Dermatomyositis

Dermatomyositis is an autoimmune inflammatory myopathy with characteristic cutaneous findings caused by small-vessel vasculitis. It involves striated muscles and skin. Often the formation of dystrophic calcifications is the result of the inflammatory episodes [10]. Soft-tissue calcification occurs most commonly in chronic Dermatomyositis, especially with onset in childhood, being uncommon in adult-onset disease [3].

Epidemiology -Clinical Presentation

There is a female predilection. There are two types of dermatomyositis: Juvenile dermatomyositis (JDM) which affects children and tends to be more severe and adult dermatomyositis (ADM) which typically affects adults around the age of 50. There are two peak ages of incidence: Childhood (5-15 years) and adulthood (50-60 years). When the disorder manifests before age 16, it is called juvenile or childhood dermatomyositis [11]. In juvenile dermatomyositis, the severity of calcinosis is irrelevant to the patient's sex and the beginning of

symptoms, although increased delay to diagnosis and treatment impair this complication [12]. Generally, calcification is noted 1 to 3 years after the onset of the disease and occurs in 25% to 50% of patient. Calcinosis may precede the myopathy [13]. Mineral deposits develop over a period of 1 to 3 years. In calcinosis universalis, calcification occurs in subcutaneous tissues, but firstly in periarticular regions or in areas that are subject to trauma. In calcinosis circumscripta, the calcifications are more localized and typically appear around joints. Symptoms such as pain and skin ulceration may limit mobility and result in skin contractures. Additionally, abscess formation is not rare. Usually the dystrophic calcification remains stable but rarely some spontaneous resolution is reported [11,14]. Dystrophic calcification is rare in adults with dermatomyositis [15].

Etiology and pathogenesis

Juvenile dermatomyositis appears to be a form of complement-mediated micro-angiopathy [16]. There seems to be an association with the HLA-DQA1*051 allele [17]. The precise cause of the dystrophic calcification, however, is unknown and it consists of hydroxyapatite crystals according to electron microscope [18]. Immune deficiencies may predispose the patient to this complication. Calcinosis seems to occur in the majority of long-term survivors and it is possible to reflect a scarring process, which is supported by the observation that mineral deposition seems to appear initially in the muscles that were most severely affected during the acute phase of the disease. There is a variety of mechanisms for the formation of dystrophic calcification, such as the release of alkaline phosphatase or discharge of free fatty acids from affected muscles that, successively, directly precipitate calcium or bind acid mucopolysaccharides. Calcium-binding proteins may be responsible for the mineral deposition, which is speculated from the creased urinary levels of gamma-carboxylated peptides. More specifically, regarding to the immunopathology of dermatomyositis, an early event in the disease is the damage to the endothelial cells of endomysial capillaries mediated by complement activation and formation of membranolytic attack complexes (MAC), which causes lysis of the endothelial cells, destruction of capillaries, and muscle ischemia. As a re-

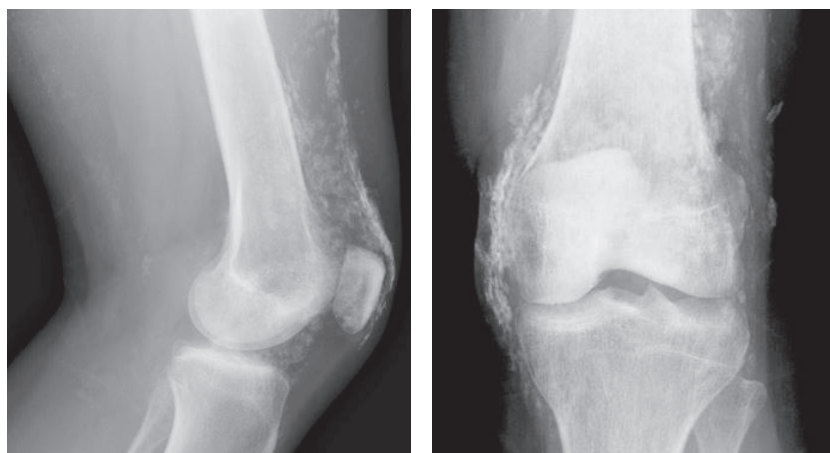


Fig.10 46 year old female with dermatomyositis and extensive soft tissue calcifications about the knee

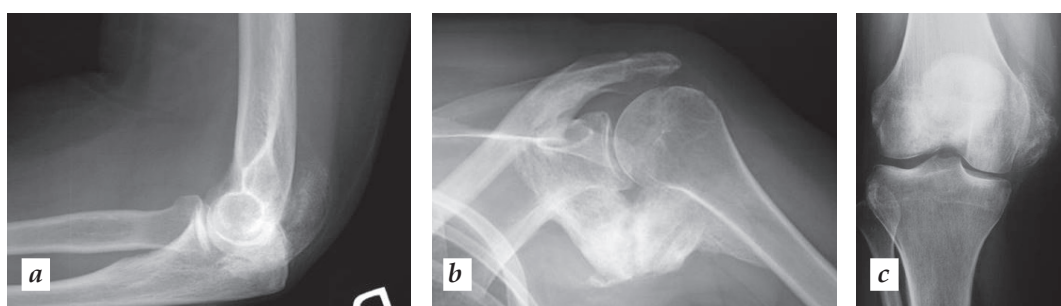


Fig.11 a,b,c 33 year old female with limited range of motion about shoulder, elbow and knee after closed head injury. Heterotopic ossification is noted at all three sites.

sult, the number of capillaries is reduced throughout the muscle, while the lumen of the remaining ones is dilated to compensate for the ischemic process. The pathology is more pronounced in the outer layers of the fascicles probably due to hypo-perfusion resulting in 'perifascicular atrophy' [19].

Laboratory Findings

Mineral metabolism in juvenile dermatomyositis has been studied. Hypercalcemia with hypercalciuria and hyperphosphaturia may occur, although these values are usually normal. Elevated levels of gamma- carboxyglutamic acid have been found in the urine of children with dermatomyositis, especially if there is calcinosis [10]. Several laboratory findings are characteristic of dermatomyositis (DM) and polymyositis (PM). These include: elevated levels of muscle enzymes [20, 21]. Autoantibodies, including antinuclear antibodies, in up to 80 percent of patients with Dermatomyositis and Polymyositis [20-23], myositis-specific autoantibodies, in

at least 30 to 40 percent of patients [24-26] and myositis-associated autoantibodies, especially in patients with overlap syndromes, elevated levels of serum and urine myoglobin [27-28]. The erythrocyte sedimentation rate (ESR) is often normal or is only mildly elevated, even in patients with active muscle disease [29].

Radiographic Findings

In juvenile dermatomyositis, four types of dystrophic calcification occur [3]:

1. Superficial masses (small circumscribed nodules or plaques) within the skin.
2. Deep discrete subcutaneous nodular conglomerations near joints that can reduce mobility (calcinosis circumscripta) (**Fig. 9**)
3. Sheet-like, linear deposits within intramuscular fascial planes (calcinosis universalis) (**Fig. 10**).
4. Reticular subcutaneous deposits that enclose the torso forming a generalized "exoskeleton".

Magnetic resonance imaging (MRI) of skeletal mus-

cles is a noninvasive sensitive but nonspecific modality for detecting areas of muscle inflammation and edema with active myositis, fibrosis and calcification [30].

Treatment

Important for minimizing the risk of calcinosis and for reserving good functional recovery is the use of high dose prednisone immediately after the onset of symptoms. If the response is incomplete, consideration is given to additional immunosuppressive agents, but their efficacy remains unclear. New agents such as monoclonal antibodies or fusion proteins that target cytokines, adhesion molecules, T-cell transduction or transmigration molecules, and B cells or their activation factors are promising immunotherapeutic agents [31]. Rituximab, a B cell-depleting agent, is currently tested in a controlled study. Combination therapy with intravenous corticosteroids and IVI may be required for the treatment of aggressive Dermatomyositis. In contrast to Polymyositis and Dermatomyositis, there is currently no effective treatment for sporadic inclusion body myositis (sIBM). The use of prednisone, cyclosporine, azathioprine, methotrexate, total body irradiation, and IFN- β didn't work as well as the use of oxandrolone. Treatment with IVIg, in some patients, caused transient improvement of muscle strength and swallowing [31]. Alemtuzumab (Campath), a T-cell-depleting monoclonal antibody, in a small and uncontrolled study, significantly slowed down disease progression for a 6-month period. Most importantly, this proof-of-principle study showed that depletion of T-cells from the periphery caused reduction of T-cells in the muscle and suppression of some degeneration-associated molecules, based on repeated muscle biopsies [32]. Phosphate-binding antacid therapy may reverse the mineral deposition [33]. In a small clinical trial, warfarin sodium treatment to decrease gamma-carboxylation was not associated with changes in calcium or phosphorus excretion or a reduction in calcinosis. Remarkable resolution of calcinosis universalis occurred in a young man treated with probenecid to improve renal handling of phosphate [34], and positive response to alendronate [35] and diltiazem has been described [36]. Surgical removal is also a solution for calcium deposits which affects patient's life.

Prognosis

The clinical course of dermatomyositis in children vary and more specifically some have long-term relapsing persistent disease, whereas others recover. Severe residual weakness, joint contractures, and calcinosis which can cause long term disability are clinical manifestations when recovery is incomplete [34]. The use of cytostatics had no visible impact on the survival of the patients. The association between dermatomyositis and malignancy has been reported in many recent studies. Studies suggest that the patient's age, the association with cancer, the delay of diagnosis and the initial dose of corticosteroids predict the prognosis of polymyositis/ dermatomyositis. However, neither the baseline levels of creatine kinase and ESR nor the use of cytotoxic drugs appeared to have any impact on the survival of these patients [37].

Heterotopic Ossification

The extraskeletal formation of bone (heterotopic ossification -HO) is noticed in patients following traumatic injuries or invasive surgeries while it is related to many congenital disorders. HO can occur almost anywhere in the human body and it can be locally or systematically appeared. Locally it is commonly seen after an injury to an area. Systematically extraskeletal calcification is a complication of paraplegia, quadriplegia or consequence after closed head injury. In these cases, ossification usually is noticed about the shoulders, elbows and hips and implies immovability and certainly reduced quality of life for the affected individuals [38]. Although several systems have been used, the Brooker classification is widely used (especially at the hip) for the classification for the severity of HO. According to Brooker classification there are five grades: **Grade 0:** no ossification present. **Grade 1:** Small bone islands are identified in the tissues around the bone. **Grade 2:** Bone spurs are identified at the pelvis and/or proximal femur. There is more than 1 cm of space between the opposing bones. **Grade 3:** Bone spurs identified at the pelvis and/or proximal femur. There is less than 1 cm of space between the opposing bones. **Grade 4:** Ankylosis present at the hip [39].



Fig.12 Post traumatic heterotopic ossification



Fig.13 Chondrocalcinosis of the articular hyaline cartilage and meniscal fibrocartilage of the knee in patients with calcium pyrophosphate dehydrate deposit

Pathophysiology

The pathogenesis of HO is not fully understood but there is a genetic predisposition. Several factors, such as prostaglandin E2, bone morphogenetic protein (BMP), and the inflammatory process, establish a major role to the development of HO [40].

Clinical presentation

The presentation of the clinical symptoms of HO may varies from 3 weeks to 12 weeks after the triggering event. The most common symptom is pain around the site of HO (common affected side is the hip). Associated features can include fever, soft

tissue swelling, and poor mobility of the affected joint [38].

Laboratory findings

Alkaline phosphatase (ALP) is used as a useful screening tool. ALP serum levels increase approximately two weeks after injury. Recently the measurement of the 24-h PGE2 urinary excretion has been recommended as a valuable indicator of early HO [38]. Also Creatine Kinase (CK) elevated serum levels correlates with the muscle involvement and it is an indicator for HO. Elevated C-reactive protein (CRP) correlates with inflammatory activity of HO.

Radiographic findings

Plain radiograph is the primary imaging method (**Fig. 11**). The typical radiologic appearance of HO is circumferential ossification with a lucent center [41] (**Fig.12**). CT is able to identify lesion mineralization earlier and has good overall specificity. There is no specific role for MRI once the diagnosis of HO has already been made. MRI is usually used in the evaluation of a soft tissue mass and for other possible causes such as neoplasms (i.e. osteosarcoma) or subjacent osteomyelitis [42].

The use of SPECT/CT is superior to other imaging methods, such as radiography and computed tomography. It is able to determine the osteoblastic activity and the maturation of HO, evaluating if resection would be safe. It is a helpful diagnostic tool for the preoperative evaluation because it helps to define which patients shall present higher risk of recrudescence after surgical resection [43].

Treatment

Prophylaxis or early treatment of heterotopic ossification is very important due to the possible complications of HO (peripheral nerve entrapment, pressure ulcers, and functional impairment) if joint ankylosis develops [44-45]. For the treatment or prophylaxis for HO, non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin, bisphosphonate (such as ethane-1-hydroxy-1,1-diphosphate), or local radiation therapy is used [38]. Indications for surgical resection are severe loss of motion and decreased function.

Chondrocalcinosis

Calcium Pyrophosphate dehydrate deposition disease (CPPD). The names used for the calcium pyrophosphate crystal-related disorders include: (a) pseudo-gout, for the acute attacks of inflammatory arthritis caused by calcium pyrophosphate crystal (CPP) deposition; (b) chondrocalcinosis, for the radiographic calcification in hyaline and/or fibrocartilage tissues; and pyrophosphate arthropathy, for the radiographic or joint abnormalities accompanying calcium (c) pyrophosphate dehydrate crystal deposition (CPPD) disease. It is a type of arthritis that, as the old name of pseudo-gout suggests, can cause symptoms similar to gout. Yet in CPPD a different type of crystals triggers the reaction. CPPD can cause bouts of severe pain and swelling in one or more joints, which can limit activity for days or weeks. The condition most often involves the knees, but can affect wrists, shoulders, ankles, elbows, hands or other joints.

The range of presentations, named as proposed by a European League Against Rheumatism (EULAR) [46] includes:

- Asymptomatic CPPD disease
- Acute CPPD crystal arthritis (pseudo-gout)
- Chronic CPPD crystal inflammatory arthritis
- Osteoarthritis with CPPD, with or without superimposed acute attacks
- Severe joint degeneration (pseudo-neuropathic joint disease)
- Spinal involvement

Epidemiology

It is either hereditary (Autosomal dominant), idiopathic or associated with various metabolic disorders. The estimation of affection of CPPD 4-7 % of the adult populations of Europe and the United States [47,48], especially in the elderly. According to one study, the average age at diagnosis of CPPD disease was 72 years [49]. There is an age-related increase in the prevalence of cartilage calcification according to radiographic surveys [50, 51]. According to age, the predominance of radiographic calcium pyrophosphate deposition, in a survey carried out in a geriatric clinic was:

- 65 to 74 years – 15 %
- 75 to 84 years – 36 %

- >84 years – Almost 50 %

The gender distribution of CPPD disease has differed among large series [49, 52, 53]. No major gender predominance appears. In men, attacks of acute arthritis are more common, while in women, atypical patterns of osteoarthritis with calcium pyrophosphate crystal deposition is usually seen.

Pathophysiology

CPP crystal formation is initiated in cartilage located near the surface of chondrocytes. There is an association with excessive cartilage pyrophosphate production, leading to local calcium pyrophosphate supersaturation and CPP crystal formation or deposition. Aberrance in both mineral and organic phase metabolism have involvement in CPPD disease [54, 55]. A definitive causative role of CPPD in all of the clinical manifestations with which deposition is associated, particularly the non-inflammatory changes, has not been established but there is compelling evidence for a role of the CPP crystal in acute and subacute joint inflammation [56-60]. There is a self-limited nature of acute attacks of CPP arthritis, which is not well understood [61, 62]. Most cases of CPPD disease are idiopathic. Joint trauma, including prior joint surgery, familial chondrocalcinosis, metabolic and endocrine disorders, including hemochromatosis are also associated with or may cause the illness, especially among the young [63]. The only disorder associated with the full spectrum of CPPD diseases is hemochromatosis [63]. Hypomagnesemia, hyperparathyroidism and hypophosphatasia have association with chondrocalcinosis as well as with acute CPP crystal arthritis but are not clearly associated with chronic CPPD arthropathy [63].

Arthroscopic-Laboratory findings

For the establishment of the diagnosis arthrocentesis of an affected joint with synovial fluid analysis for CPP crystals should be undertaken if possible. The presence of positively birefringent CPP crystals by compensated polarized light microscopy is the most prominent finding. Phagocytosed crystals within polymorphonuclear leukocytes are virtually always present in inflamed joints during an attack of acute CPP crystal arthritis. Total synovial fluid leukocyte concentration in an acute



Fig.14 Synovial osteochondromatosis in a 24-year-old man with hip pain. Multiple small, dense, punctate calcifications

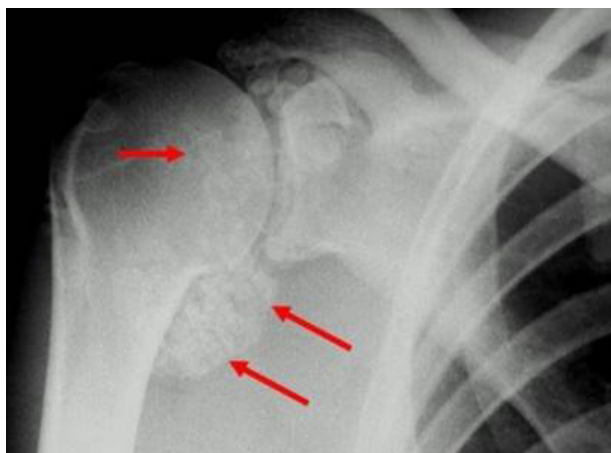


Fig.15 Synovial osteochondromatosis in a 30-year-old man with shoulder pain. Multiple small, dense, punctate calcifications and loose bodies

attack is typically 15,000 to 30,000 per mm^3 , 90 percent of which are neutrophils. In chronically symptomatic joints, cell counts are typically lower and also crystals are often found extracellularly. The number of CPP crystals in the synovial fluid is related to the degree of clinically apparent inflammation [64] and the proportion of intracellular crystals correlates roughly with the level of inflammation (as reflected clinically and by the

synovial fluid neutrophil concentration). In some cases, CPP crystals are too small to be visualized [65]. The coexistence of urate and CPP crystals in a single inflammatory effusion is neither uncommon nor unexpected, given the observed frequencies of hyperuricemia and gout among patients with CPPD disease [64].

Radiographic findings

Plain film radiography, which depicts findings of cartilage calcification, is the imaging evidence for CPPD. Among affected fibrocartilages in CPPD disease are the menisci of the knee (usually bilaterally) (**Fig.13**), the symphysis pubis, the triangular discs of the wrist joints, and the glenoid and acetabular labra. CPP crystal deposits in hyaline cartilage usually appears as a radiopaque line paralleling the surface of the underlying bone. Degenerative changes in the joint are also frequently present. Larger joints, such as the knee, wrist, elbow, shoulder, and hip, are most frequently involved in CPPD disease, but almost any diarthrodial joint may be affected radiographically. Articular capsule or synovial calcification is often fainter and more diffuse than cartilage calcification. Linear calcifications involving the Achilles tendon or plantar fascia are often seen in CPPD disease [66]. Ultrasonography findings that correlate with radiographic features of CPPD disease have also been described. Magnetic resonance imaging (MRI) is a less sensitive imaging modality for documenting CPP crystal deposition than plain film radiography, ultrasonography, or computed tomography (CT).

Treatment

No treatment is available to dissolve the crystal deposits. Treatment strategies are supported from the aforementioned European League Against Rheumatism (EULAR) panel based on a careful analysis of the literature [46, 47]. In patients with acute CPP crystal arthritis with no more than two acutely inflamed joints as initial treatment is suggested joint aspiration and intraarticular glucocorticoid injection rather than oral agents. In patients with features suggesting joint infection, glucocorticoid injection is postponed until infection is excluded by synovial fluid Gram stain and culture, and treat as in patients who are unable to undergo arthrocente-

sis. In patients with acute CPP crystal arthritis who are not treated with arthrocentesis and injection, oral anti-inflammatory therapy is suggested with: A non-steroidal anti-inflammatory drug or oral colchicine in a low-dose regimen or an oral glucocorticoid, such as prednisone. Parenteral glucocorticoids may be used when oral glucocorticoid therapy is ineffective or not obtainable. In patients with acute CPP crystal arthritis in whom oral anti-inflammatory treatment is initiated within 24 hours of flare onset, low-dose oral colchicine is prescribed rather than an NSAID or an oral glucocorticoid [67]. For patients with three or more attacks of acute CPP crystal arthritis annually prophylaxis with colchicine is suggested rather than limiting treatment to the period of each acute attack. Appropriate dose adjustment for renal and hepatic dysfunction, drug intolerance, and potential drug interactions is necessary [68]. In chronic CPP crystal inflammatory arthritis, NSAIDs and/or colchicine are used. If needed hydroxychloroquine (HCQ), low-dose glucocorticoids, and methotrexate (MTX) can be used also. Surgery to repair and replace damaged joints is an option in severe cases [69-71].

Synovial chondromatosis

Synovial chondromatosis is a relatively common disorder characterized by loose cartilaginous bodies. It is caused by a metaplasia of the synovium and results in deposition of cartilaginous foci in the joint which may or may not be calcified. Up to 30% of the time, the cartilaginous deposits do not calcify [72]. It is classified under two main types:

1. Primary synovial chondromatosis: principally mono - articular disorder of unknown aetiology
2. Secondary synovial chondromatosis: resulting in intra - articular loose bodies after trauma or from causes such as osteoarthritis and neuropathic arthropathy.

Epidemiology

Primary synovial chondromatosis typically affects adults, predominantly men, in the third to fifth decades of life. Any synovium-lined joint may be affected. Most commonly affects knee, hip and shoulder joint. It tends to be mono-articular. Knee is the most commonly affected site [73].

Histopathology

Primary synovial chondromatosis histopathologically is characterized by hyperplastic synovium covering bluish white, multilobulated, nodular projections of hyaline cartilage diffusely which involves the entire joint surface [74-75]. These nodules may be multiple and give a "cobblestone" appearance to the synovium. The extension of sub-synovial lobular nodules of hyaline into adjacent soft tissues and bursae is possible. Also they may extrinsically erode bone. The pathologic appearance of extra-articular (tenosynovial or bursal) chondromatosis is similar to that of intraarticular disease, but extra-articular disease involves the subsynovium that extends about bursae or along tendon sheaths [76]. The subsynovial nodules of hyaline cartilage may distract from the synovium to lie within the joint, bursa, or tendon sheath. They may reconnect to the synovium and be reabsorbed or be loose within the affected space.

Clinical Presentation

Patients present with pain, swelling and limited range of motion of the affected joint. Physical examination depicts diffuse joint swelling and enlargement, articular tenderness, articular crepitus, locking and palpable nodules or a mass. Associated muscle atrophy has been reported. At the onset of the disease symptoms are often insidious and gradually they progress. Rare spontaneous regression is also reported [77]. The duration of clinical symptoms before diagnosis is often long, with an average of 5 years.

Imaging findings

Radiologic findings are frequently pathognomonic. Radiographs reveal multiple intraarticular calcifications (70%-95% of cases) of similar size and shape, distributed throughout the joint, with typical "ring-and-arc" chondroid mineralization (**Fig.14, 15**). Extrinsic erosion of bone is seen in 20%-50% of cases [78]. Computed tomography (CT) optimally depicts the calcified intraarticular fragments and extrinsic bone erosion. Magnetic resonance (MR) imaging findings are more variable, depending on the degree of mineralization, although the most common pattern (77% of cases) reveals low to intermediate signal intensity with T1-weighting and very high signal intensity with T2-weighting with hy-

po-intense calcifications. These signal intensity characteristics on MR images and low attenuation of the non-mineralized regions on CT scans reflect the high water content of the cartilaginous lesions. CT and MR imaging depict the extent of the synovial disease (particularly surrounding soft-tissue involvement) and lobular growth [78]. Secondary synovial chondromatosis can be distinguished from primary disease both radiologically (underlying articular disease and fewer chondral bodies of variable size and shape) and pathologically (concentric rings of growth).

Treatment

Treatment of choice for primary synovial chondromatosis is surgical synovectomy with removal of chondral fragments [78]. Recurrence is not unusual and may be related to incomplete resection. Arthroscopic treatment has been used successfully in the knee, hip, elbow, shoulder and the subacromial bursa with very low recurrence rates. Arthroscopic techniques can not treat extra-articular disease which has been noted in 21%-80% of cases [79, 80]. Local recurrences can be treated effectively with additional surgical intervention. Malignant transformation of primary synovial chondromatosis to chondrosarcoma is unusual and can be difficult to distinguish from benign disease, both pathologically and radiologically. Multiple recurrences with development of marrow invasion should be viewed as representing malignant transformation [78].

Fibrodysplasia (Myositis) Ossificans Progressiva

Fibrodysplasia ossificans progressiva (FOP), also called myositis progressive, is a rare heritable connective tissue disease characterized by (a) congenital malformation of the great toes, and (b) recurrent episodes of painful soft tissue swelling that lead to heterotopic ossification [81]. Posttraumatic myositis ossificans, a different disorder, also features bone and cartilage formation within soft tissues. In this sporadic condition, injured sites may initially be painful, warm, and feel “doughy”, but 4 to 6 weeks later, they contain mineralization that is apparent radiographically. Heterotopic ossification also may follow hip and spinal cord injury.

Epidemiology

FOP is very rare with a worldwide prevalence of approximately 1 case in 2 million individuals. No ethnic, racial, or geographic predisposition has been described [82].

Clinical Presentation

If the typical congenital skeletal malformations are recognized, FOP should be suspected at birth before soft-tissue lesions occur. The characteristic feature is short big toes caused by malformation (hallux valgus) of the cartilaginous anlage of the first metatarsal and proximal phalanx. In some patients, the thumbs are also strikingly short. Synostosis and hypoplasia of the phalanges is typical. Nevertheless, the digital anomalies are not pathognomic. FOP is usually diagnosed when soft-tissue swellings and radiographic evidence of heterotopic ossification are first noted. The severity of FOP differs significantly among patients, although most become immobilized and confined to a wheelchair by the third decade of life [83]. Typically, episodes of soft-tissue swelling begin during the first decade. Occasionally, the onset is as late as early adulthood. There are also reports of in utero involvement. Painful, tender, and rubbery soft-tissue lesions appear spontaneously or may seem to be precipitated by minor trauma including intramuscular injections. Swellings develop rapidly during the course of the several days. Fever may occur during periods of induration and can erroneously suggest an infectious process. Typically, lesions affect the paraspinal muscles in the back or in the limb girdles and may persist for several months. Aponeuroses, fascia, tendons, ligaments, and connective tissue of voluntary muscles may be affected. Although some swellings may regress spontaneously, most mature through an endochondral pathway, engendering true heterotopic bone.

Gradually, bone masses immobilize joints and cause contractures and deformity, particularly in the neck and shoulders. Ossification around the hips, typically present by the third decade of life, often prevents ambulation. Ankylosis of the spine and rib cage further restricts mobility and may imperil cardiopulmonary function. Scoliosis is common and

associated with heterotopic bone that asymmetricaly connects the rib cage to the pelvis. Hypokyphosis results from ossification of the paravertebral musculature. Restrictive lung disease with predisposition to pneumonia may follow. However, the vocal muscles, diaphragm, extraocular muscles, heart, and smooth muscles are characteristically spared. Although secondary amenorrhea may develop, reproduction reproduction may occur. Hearing impairment (beginning in late childhood or adolescent) and alopecia also manifest with increased frequency.

Radiologic features

Skeletal adnormalities instead of anomalies and soft-tissue ossification are the characteristic radiographic features of FOP. The principal malformations involve the great toe, although other toes are frequent. A remarkable feature of FOP is progressive fusion of cervical vertebrae that may be confused with Klippel-Feil syndrome or Still's disease. The femoral necks may be broad yet short. However, the remainder of the skeleton is unremarkable. Ectopic ossification in FOP progresses in several regular patterns or gradients (proximally before distally, axially before appendicularly, cranially before caudally, and dorsally before ventrally). Paraspinal muscles are involved early in life, with subsequent spread to the shoulders and hips. The ankles, wrists and jaw may be affected later. Radiographic and bone scan findings suggest normal modeling and remodeling of heterotopic bone. Fractures are not increased but respond similarly in either the heterotopic or normotopic skeleton. Bone scans are abnormal before ossification and can be demonstrated before conventional radiography findings. Computerized tomography and magnetic resonance imaging of early lesions has been described.

Laboratory Findings

Routine biochemical studies of mineral metabolism are usually normal, although alkaline phosphatase activity in serum may be increased, especially during disease "flare-ups". Urinary basic fibroblast growth factor levels may be elevated during disease flare-ups coinciding with the pre-osseous angiogenic phase of fibro-proliferative lesions [84].

Histopathology

The earliest FOP consists of significant aggregation of B and T lymphocytes in perivascular spaces of otherwise normal-appearing skeletal muscle. Subsequently, a nearly pure T-cell infiltrate is seen between edematous muscle fibers at the leading edge of an angiogenic fibro-proliferative lesion, which is indistinguishable from aggressive juvenile fibromatosis. Misdiagnosis is common, but can be avoided by examining the patient's toes [83].

Etiology and Pathogenesis

The genetic defect causing FOP has not been mapped. Dysregulation of BMP4 gene expression has been reported, but mutational screening and linkage-exclusion analysis indicate that the molecular defect lies elsewhere [84].

Treatment

There is no established medical treatment for FOP. The disorder's rarity, variable severity and fluctuating clinical course pose substantial uncertainties when evaluating experimental therapies. Adrenocorticotrophic hormone (ACTH), corticosteroids, binders of dietary calcium, intravenous infusion of ethylene-diamine-tetra-acetic acid (EDTA), nonsteroidal anti-inflammatory agents, radiotherapy, disodium etidronate, and warfarin are ineffective. Limited benefits have been reported using corticosteroids and disodium etidronate together during flare ups and by using isotretinoin to prevent disease activation. However, these impressions represent uncontrolled studies. Accordingly, medical intervention is currently supportive. Nevertheless, physical therapy to maintain joint mobility may be harmful by provoking or exacerbating lesions. Surgical release of joint contractures is unsuccessful and risks new, trauma-induced heterotopic ossification. Removal of FOP lesions is often followed by significant recurrence. Osteotomy of ectopic bone to mobilize a joint is uniformly counterproductive because additional heterotopic ossification develops at the operative site. Spinal bracing is ineffective, and surgical intervention is associated with numerous complications [83]. Measures against recurrent pulmonary in-



Fig.16 *Calcinosis circumscripta. Radiograph of the hand show multiple, punctate calcifications in the soft tissue characteristic of calcinosis circumscripta. The patient had a 10 year history of scleroderma*

fections and the onset of cardiopulmonary complications of restrictive lung disease are important.

C. Calcinosis

Calcinosis is the calcification of cutaneous, subcutaneous or deep connective tissue and it is not associated with metabolic disturbance while it may be associated with collagen-vascular disease. It is divided in three types:

1. Calcinosis Circumscripta
2. Calcinosis Universalis
3. Tumoral calcinosis

1. Calcinosis circumscripta

Calcinosis circumscripta (CC) is a local form of calcinosis and it is characterized by the deposition of calcium in the subcutaneous tissues, muscles and fascia.

Clinical presentation

Usually skin and subcutaneous tissues are affected, mainly the upper limbs and especially the fingers [85]. It occurs in the periarticular area as a painful mass with surrounding erythema and edema. Patients present with firm white dermal papules, plaques or subcutaneous nodules.

Ulceration is possible as well as extrusion of a chalky white material. It is visible in x-rays as localized, scattered calcification.



Fig.17 *Calcinosis universalis. Diffuse cutaneous, subcutaneous and muscular calcification*

Epidemiology

There is a predilection in women (male to female ratio of 1:6) and occurs mainly in adult, rarely in children [86].

Aetiology

The etiology is unknown. It is a condition usually associated with scleroderma, Raynaud's disease, and telangiectasia [85].

Radiographic Finding

The most common finding is fine clustered calcifications, usually around the finger and toe tips (**Fig.16**). In case of an associated underlying disease soft tissue swelling and joint arthropathy may be present. Features that distinguish CC from tumoral calcinosis include the extent of calcification, which is generally less in CC, and the distribution of calcification in the subcutaneous tissues rather than in bursal regions. Otherwise, the radiographic appearances are similar [85].

Treatment

There is no specific treatment described for calcinosis. Some attempts have aimed at preventing further deposition of calcium and reabsorbing existing deposits. Restricted calcium diets have shown little success. Drugs such as calcium disodium edentate, acetylcholine, parathyroid extract, insulin and pilocarpine have also proven to be ineffective. Locally, the lesions can be removed,

particularly when occurring over a joint and restricting function; however, as the condition resolves spontaneously it is difficult to advocate this. Some researchers have reported local removal of calcium deposits to be ineffective [85].

2. Calcinosis universalis

Calcinosis universalis (CU) is a rare disease characterized by the deposit of calcium in the skin, in the subcutaneous cellular tissue, and also in the tendinous and muscle tissues.

Epidemiology

Most cases become apparent during the first decade of life.

Clinical presentation

Clinical aspects may vary from arthralgia to movement limitation, with calcification of soft tissues. Fatigue, muscle pain and stiffness could be present. Palpable calcific plaques in subcutaneous or deeper tissue are usual findings. One third of cases are associated with scleroderma, dermatomyositis, - polymyositis, and systemic lupus erythematosus. Differential diagnosis should exclude fibrodysplasia ossificans progressive, progressive osseous heterodysplasia, myositis ossificans and dermatopolymyositis.

Laboratory findings

The diagnosis is difficult and usually made by exclusion. Laboratory results show normal serum and urinary calcium and phosphorus concentrations, normal hepatic and renal function, and normal complement values. The results for lupus erythematosus cells, anti-nuclear and anti-DNA antibodies are negative [2]. High rates of hemosedimentation and microcytic and hypochromic anemia may be found [87].

Radiographic findings

The radiographs showed calcifications of various sizes, linear or nodular, usually bilateral (87). The characteristic sheet like distribution of CU and its involvement of muscle and fascial planes usually makes this condition distinct from tumoral calcinosis at imaging [88] (Fig.17).

Treatment

There is no specific treatment, but the use of calcium chelates (EDTA), bisphosphonates (disodium etidronate) and steroids [87].

Prognosis

CU is a chronic disease characterized by a poor prognosis [87].

3. Tumoral calcinosis

Tumoral calcinosis (TC) is a rare entity characterized by calcium salt deposition in different peri-articular soft tissue regions. The classic TC masses are densely lobular calcified lesions confined to the soft tissue, commonly at the extensor surface of the joint in the anatomic distribution of a bursa. In descending order, the most common locations are the hip, elbow, shoulder, foot, and wrist. Visceral calcification does not occur, but segments of vasculature may contain mineral deposits. There are two types of TC, according to the presence or absence of an underlying calcifying disease process. TC has been divided into primary (idiopathic) and secondary. Two subtypes of the primary variety exist; a hyper-phosphatemic type and a normo-phosphatemic type. The secondary variety is mainly associated with chronic renal failure and the resulting secondary or tertiary hyperparathyroidism [89].

Epidemiology

There is familial tendency and no sex predominance. Also there is a significantly higher incidence in patients of African descent. Lesions primarily proliferate during the first 2 decades of life. In many patients hyperphosphatemia is a pathogenic factor [88].

Clinical Presentation

The soft tissue tumors of ectopic calcification are typically painless and grow at variable rates. The major clinical complications of TC are due to metastatic calcification that occurs around joints and in skin, marrow, teeth and blood vessels. Frequently they are lobulated, and firmly attached to deep fascia. Occasionally the swellings infiltrate into muscles and tendons [5]. Because the deposits are extracapsular, joint range of motion is not impaired unless the tumors are particularly large. There can, however, be compression of ad-

jacent neural structures. The lesions also can ulcerate the skin and form a sinus tract that drains a chalky fluid; this may lead to infection. Other potential secondary problems include anemia, low-grade fever, regional lymphadenopathy, splenomegaly, and amyloidosis. Some patients have features of pseudoxanthoma elasticum (i.e. skin and vascular calcifications and angeoid streaks in the retina). A dental abnormality, featuring short bulbous roots and calcific deposits that often obliterate pulp chambers, is a characteristic finding [2, 8].

Diagnosis

TC appears in radiographs as an amorphous, cystic, and multi-lobulated calcification located in a periarticular distribution. CT findings are similar to that of plain radiography, but with more clarity to the lesion. Cystic components may show a layer of calcium within them, which is known as the “sedimentation sign” [88]. Erosion or osseous destruction by adjacent soft-tissue masses is absent. Despite the calcification magnetic resonance imaging, T2-weighted sequences show inhomogeneous high-signal-intensity and T1-weighted sequences show inhomogeneous low-signal intensity lesions. Two patterns are generally observed: (a) a diffuse, lower-signal-intensity pattern or (b) a bright, nodular pattern with alternating areas of high signal intensity and signal void. Martinez, et al. [90] discovered additional radiologic features, primarily bone marrow involvement, which demonstrates a periosteal reaction on radiographs and increased radionuclide uptake at bone scintigraphy. Cerebral and peripheral aneurysms have been also identified in patients with TC. TC has extensive variation in appearance and can be confused with other soft-tissue calcifications. The differential diagnosis of TC includes calcific tendonitis, calcinosis of chronic renal failure, calcinosis universalis, calcinosis circumscripta, synovial osteochondromatosis, synovial sarcoma, osteosarcoma, myositis ossificans, tophaceous gout as well as calcific myonecrosis.

Laboratory Findings


Serum Calcium levels and alkaline phosphatase activity are usually normal. Hyperphosphatemia and in-

creased serum calcitriol levels occur in some patients. The phosphate transport maximum/ glomerular filtration rate (TmP/FGR) may be supranormal but renal function is otherwise unremarkable. Patients are in positive calcium/ phosphate balance. Renal studies reflect both the ongoing calcium and phosphate retention, and some patients are frankly hypo-calciuric. The chalky fluid found in lesions is predominantly hydroxyapatite.

Treatment

The treatment of TC should be according to the type of the lesion, stage of the pathology as well as with the site, size, relations of the lesion and the symptoms of the patient [89]. Surgical resection of the calcified mass is the main treatment for the primary type, but should be avoided in hemodialysis-related types, which are instead often treated with parathyroidectomy [91]. Surgical removal of subcutaneous calcified masses may be helpful if they are painful, interfere with function, or are cosmetically unacceptable. Administration of steroids, diphosphonates, or calcitonin and radiation therapy have not proven to be effective. Treatment of secondary TC is mainly medical and includes calcium and phosphorus restricted diets, dialysates, and phosphate binders (except aluminum containing binders). Several other medical treatments including Vinpocetine, Sodium thiosulfate, intravenous Pamidronate, have been used in treatment of the secondary TC. Subtotal or total parathyroidectomy in case of underlying secondary or tertiary hyperparathyroidism and kidney transplantation in case of end stage renal disease-related or hemodialysis-related TC may also be considered [89].

Prognosis

Despite widespread heterotopic ossification and severe disability, some patients live up to their seventh decade of life the seventh decade. Most, however, die earlier because of pulmonary complications, including pneumonia, secondary to restricted ventilation from chest-wall involvement. 

Conflict of interest:

The authors declared no conflicts of interest.

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ΠΕΡΙΛΗΨΗ

Οι εξωσκελετικές ασβεστώσεις αποτελούν συχνό απεικονιστικό εύρημα. Η αναγνώρισή τους και η συσχέτισή τους με νοσολογικές οντότητες και μεταβολικά νοσήματα του μυοσκελετικού συστήματος είναι σημαντική. Η ταξινόμηση των παθήσεων με εξωσκελετική εναπόθεση ασβεστίου και φωσφόρου περιλαμβάνει τρεις κύριες κατηγορίες: (1) την μεταστατική ασβεστοποίηση, (2) τη δυστροφική ασβεστοποίηση, και (3) την ασβέστωση. Η μεταστατική ασβεστοποίηση αναπτύσσεται στις περιπτώσεις παθολογικής αύξησης των επιπέδων ασβεστίου και φωσφόρου στο αίμα με αποτέλεσμα την εναπόθεσή τους σε διάφορους ιστούς. Στις παθήσεις που προκαλούν μεταστατική ασβεστοποίηση περιλαμβάνονται ο υπερπαραθυρεοειδισμός, οι νεοπλασίες, η υπερβιταμίνωση D και το σύνδρομο γάλατος-αλκάλειας. Η δυστροφική ασβεστοποίηση εμφανίζεται σε εκφυλιστικούς ή νεκρωτικούς ιστούς χωρίς να υπάρχει διαταραχή της ομοιοστασίας ασβεστίου – φωσφόρου. Σχετίζεται με μεγάλο αριθμό παθήσεων όπως αγγειακή ανεπάρκεια, κοκκιωματώδη νοσήματα, κυστικέρκωση, νεοπλασίες των οστών, σκληρόδερμα, δερματομυοσίτιδα, σύνδρομο CREST, αλλά αναπτύσσεται και μετά από τραυματισμό ενός ιστού (έκτοπη οστεοποίηση).

Η ασβέστωση αποτελεί μια ξεχωριστή μορφή εξωσκελετικής ασβεστοποίησης που συνήθως συμβαίνει στο δέρμα και σε υποδόριους ιστούς, συνήθως δεν παρουσιάζεται διαταραχή της ομοιοστασίας του ασβεστίου και φωσφόρου ενώ σχετίζεται με φλεγμονώδη νοσήματα του συνδετικού ιστού και των αγγείων.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: ασβεστοποίηση, ασβέστωση, εξωσκελετικές εναποθέσεις ασβεστίου και φωσφόρου

The combined intrarticular/intravenous administration of tranexamic acid in cemented total knee arthroplasty

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ABSTRACT

Total knee and hip arthroplasty is the commonest reason for transfusion in patients undergoing elective surgery and accounts for 9.8% of all transfused red blood cell units. However, Blood transfusions are associated with increased risks of immunological reactions, transmission of diseases and infections. In recent years pharmacological agents become more popular in management of perioperative and postoperative bleeding. Tranexamic acid (TXA), a synthetic analogue of the amino acid lysine, is a fibrinolysis inhibitor which acts by blocking the lysine binding site of plasminogen that induces blood loss. The purpose of this study was to evaluate the efficacy of combined intravenous and intra-articular administration of TXA in regard to postoperative blood loss and transfusion requirements following TKA.

KEY WORDS: total knee arthroplasty; blood loss; blood transfusion; tranexamic acid

Introduction

Total knee arthroplasty (TKA) is one of the most common surgical procedures for patients with advanced osteoarthritis. Incidence rate of TKA is expected to increase by 69% in 2050 compared to 2012 [1]. Although TKA relieves knee pain, improves function and patient's quality of life, perioperative bleeding remains one of the main concerns [2]. Total knee and hip arthroplasty is the commonest reason for transfusion in patients undergoing elective surgery and accounts for 9.8% of all transfused red

blood cell units [3]. Blood transfusions are associated with increased risks of immunological reactions, transmission of diseases and infections [4]. In recent years pharmacological agents become more popular in management of perioperative and postoperative bleeding. Tranexamic acid (TXA), a synthetic analogue of the amino acid lysine, is a fibrinolysis inhibitor which acts by blocking the lysine binding site of plasminogen that induces blood loss [5]. Recent studies and meta-analysis have shown that TXA can reduce the amount of drainage, total blood

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loss and requirement of allogenic transfusion in TKA, without increasing the risk of adverse events such as thromboembolic complications [6]. However it is not established which administration route is more effective. Various dosing regimens have been used for TXA, including intravenous (IV), intra-articular (IA) and combined application of TXA (IV and IA).

Thus, the purpose of this study was to evaluate the efficacy of combined intravenous and intra-articular administration of TXA in regard to postoperative blood loss and transfusion requirements following TKA.

Material and methods

A prospective randomized controlled study was conducted from March 2014 until March 2017. Patients with a diagnosis of primary osteoarthritis undergoing unilateral TKA and able to give informed consent were eligible for inclusion in the study. The exclusion criteria were as follows: allergy to TXA, history of previous surgery on the operated knee, thrombocytopenia, and anemia [hemoglobin (Hb) <10 g/dl], warfarin therapy, coagulopathy, VTE, or major comorbidities (ischemic heart disease, cerebrovascular accident, liver cirrhosis, end-stage renal disease). Written informed consent was obtained from all patients. A total of 172 patients were enrolled in the study and divided into four groups. The randomization concluded with 65 patients in group A (35 females and 30 males), 33 patients in group B (23 females and 10 males), 44 in group C (28 females and 16 males) and 30 patients in group D (18 females and 12 males) with similar demographic characteristics (age, BMI, severity of osteoarthritis, knee angle deformation, ASA). In group A (intra-articular (IA) group) were introduced intraarticular through the drainage 20 ml of saline solution, containing 1,000 mg of tranexamic acid. The patients who were randomized into group B (intravenous (IV) group) received administration of TXA 10 mg/kg intravenously during the induction of anesthesia and before inflation of the tourniquet. Patients assigned to group C (combined group) were given 10 mg/kg tranexamic acid intravenously dur-

ing the induction of anesthesia and before inflation of the tourniquet and intraarticular through the drainage 20 ml of saline solution, containing 1,000 mg of tranexamic acid. In group D (control group) patients received 20 mL of normal saline using intraarticular application intraoperatively after joint capsule closure and normal saline intravenously during the induction of anesthesia.

All surgical procedures were performed by the same surgical team using the standard medial parapatellar approach and under spinal anesthesia. All TKAs were unilateral and were cemented using the same prosthesis (EVOLUTION™ Medial pivot knee-WrightR). An intramedullary alignment rod was used for femoral preparation and an extramedullary guide system for tibia preparation. A tourniquet was inflated to a pressure of 300 mmHg before the incision. The tourniquet was not released until skin closure and the application of a compressive dressing. One intra-articular drain was used with open drainage (i.e., without compression of the bag) during the first 48 h after surgery. The drain remained closed for 2 hours postoperatively and subsequently the amount of drain blood loss was recorded. The drains were removed on the second postoperative day (POD) no matter what the drain output was. The postoperative rehabilitation program included continuous passive motion of the knee and muscle strengthening exercise after returning to the ward, and routine mobilization on the first POD. In order to prevent venous thromboembolic event, LMWH was given on the first postoperative day and for duration of 30 days after surgery. The criteria for discharge were a clean wound without discharge and the ability to walk with walker support.

Preoperative data including Hb levels, hematocrit (Hct) levels, prothrombin time (PT), activated partial thromboplastin time (APTT), and platelet count were collected. Outcome measurements included postoperative Hct/Hb levels, Hct/Hb drop, total drain amount, total blood loss, and transfusion rate. We checked Hb level on post-operative day (POD) 1 until 4. We assumed that the blood volume was normalized on POD 4. Total Hb loss was calculated by

TABLE 1. *Study Groups*

	Group A (TRX IA)	Group B (TRX IV)	Group C (TRX COMP)	Group (control)
Age	71.3 years (range 69-82)	70.7 years (range 35-80)	73.9 years (range 63-80)	70.3 years (range 40-87)
Sex	35 Female/30Male	23 Female/10Male	28 Female/16Male	18 Female/12Male
BMI	29.5	32	35	29.4
TKA	65	33	44	30

TABLE 2. *P values of confronting groups*

Combine vs. Intravenous	<i>t</i>	4.05
	<i>p</i>	0.0022
Combine vs. Intraarticular	<i>t</i>	1.41
	<i>p</i>	0.18
Combine vs. Control	<i>t</i>	7.56
	<i>p</i>	1.90E-05
Intravenous vs. Control	<i>t</i>	8.72
	<i>p</i>	0.00001
Intraarticular vs. Control	<i>t</i>	0.848
	<i>p</i>	0.00001

subtracting the Hb level on POD 4 from the preoperative level. Total blood loss was calculated from the maximum Hb loss and the amount of blood transfusion. Blood loss was calculated by subtracting the amount of drainage from total blood loss. The hemoglobin cut-off value for allogenic blood transfusion was 8 g/dl in symptomatic patients. All patients were screened for deep vein thrombosis using the clinical symptoms including the presence of Homan's sign and lower leg swelling for 90 days postoperative.

Statistical analyses were performed using SPSS Software (Version 20.0 for Windows, IBM Corp, Ar-

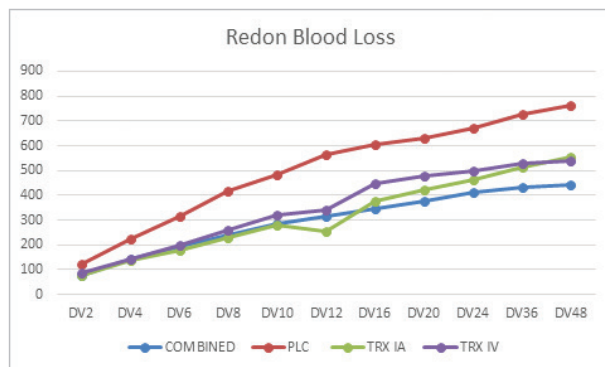
monk, NY, USA), and p values less than 0.05 were considered significant.

Results

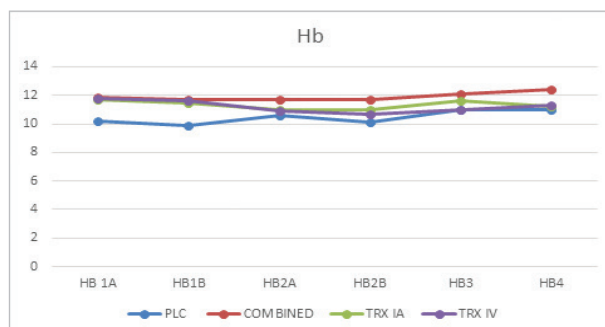
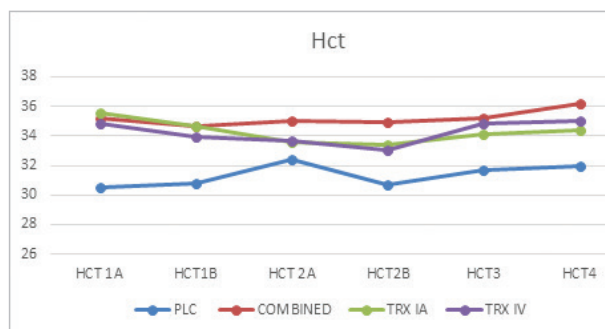
One hundred and seventy two patients were enrolled and completed the study. The demographic data are presented in **table 1**. There was no significant difference in demographic data between the groups. The mean blood loss was calculated with Burke's formula in group A 29.1%, group B 30%, group D 33.6% and group C 13.2%. The difference was statistically significant for the combined administration of tranexamic acid. Total drain amount was significantly lower in the combined group compared to the IV and control group but **not to the intraarticular group (Table 2, Graphic 1)**. Significant differences were also observed in total drain amount between IA or IV administration of tranexamic acid and control group as presented in **table 3**. More precisely the mean values of total drain amount in combined group was 440mL while for group A (IA group), group B (IV group) and group D (control group) were 554.2, 537 and 763 mL, respectively. Likewise, the minimum Hb level was recorded on postoperative day 2 for all four groups and the mean values were 11.2 g/dL in group A, 11.3 g/dL in group B, 12.4 g/dL in group C and 11 g/dL in group D (**Graphic 2, 3**). Finally one patient in the group B (IV group) and two patients in the control group D received transfusion with 1 unit of red blood cells during hospitalization. No thromboembolic complications were observed within 90 days postoperatively.

TABLE 3. Postoperative Hct/Hb variations and redon blood loss

	Group A (TRX IA)	Group B (TRX IV)	Group C (TRX COMP)	Group D (Control)
Blood loss (Redon 48h)	554.2 cc	537 cc	440 cc	763 cc
Lower M. Hct/Hb	33.4/11	33/10.7	34.9/11.7	30.5/9.9
Discharged M. Hct/Hb	34.4/11.2	35/11.3	36.2/12.4	32/11
Transfusions	1	0	0	2



Graphic 1: Redon catheter blood loss during 48h of hospitalization



Graphic 2: Variations of Hct and Hb during 48h hospitalization


Discussion

Total knee arthroplasty may be associated post-operatively with considerable blood loss and the need of transfusion is associated with risk of immunologic reactions and disease transmission with additional costs [7, 8]. The use of tranexamic acid through any route of administration (intravenous (IV), intraarticular (IA) and combined) reduce the need of blood transfusion after total knee arthroplasty without any symptomatic thromboembolic complications [9, 10]. However the ideal route of administration remains debatable. The main finding of this study was the significantly reduced total blood loss noted for combined IV and IA TXA compared with IV or IA TXA monotherapy and placebo. Our study confirms that the combination of IA and IV administration of TXA seems to be more efficient in management of perioperative and postoperative bleeding. Moreover, TXA use is safe regarding the incidence of symptomatic DVT and PE. Theoretically drainage clamping can result in temporary hemostasis while no-clamping leads to control of the hematoma formation, edema and swelling of the knee. When tranexamic acid was administrated no need of postoperative drainage clamping was required [11]. Conservation of blood products, reduced laboratory costs, and shorter hospital stays are likely advantages associated with TXA use, driving cost savings [12, 13]. In our study postoperative hemorrhage and blood loss were significantly reduced using combined intravenous and intraarticular administration of tranexamic acid. Specifically, combined administration of tranexamic acid

in patients undergoing total knee arthroplasty was associated with significantly reduced total blood loss, transfusion requirements, postoperative hemoglobin decline and length of stay compared to single application alone. Nonetheless, it was not associated with prolonged operation time. Moreover, no adverse effects, such as superficial infection, deep vein thrombosis or pulmonary embolism, were observed with tranexamic acid use. It has been suggested by the literature that combined administration of TXA demonstrated excellent clinical efficacy and safety in patients with total knee arthroplasty [14]. The clamping of drain combined with tranexamic acid administration could reduce postoperative blood loss and blood transfusion after TKA, significantly more than using tranexamic acid or drain clamping alone. There were some limitations in this study. First, no ultrasonography was done to assess asymptomatic deep vein thrombosis, nor routine screening for

pulmonary embolism. However, all patients were screened for thromboembolic complications based on their clinical symptoms during follow-up. Second, patients receiving anticoagulants were excluded from the study and thus our results cannot be expanded on those patients. Finally, there was high female-to-male ratio, because most patients who undergo TKA in Greece are female, nevertheless the female-to-male ratio was not different between the four groups.

Conclusion

The use of intraarticular in combination with intravenous administration of tranexamic acid is an efficient and safe method to control postoperative blood loss, hemorrhage and minor bleeding complications. 

Conflict of interest:

The authors declared no conflicts of interest.

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ΠΕΡΙΛΗΨΗ

Η ολική αρthroπλαστική γόνατος είναι μια από τις συχνότερα πραγματοποιούμενες ορθοπαιδικές επεμβάσεις κατά την οποία απαιτείται η μετάγγιση αίματος λόγω της απώλειας που συμβαίνει διεγχειρητικά και άμεσα μετεγχειρητικά. Δεδομένων των προβλημάτων που μπορεί να προκύψουν από την ετερόλογη μετάγγιση αίματος όπως ανοσοαντιδράσεις, μετάδοση νοσημάτων και λοιμώξεων, και των δυσκολιών που προκύπτουν από την αυτόλογη παρακαταθήκη αίματος, η χρήση του τρανεξαμικού οξέος διεγχειρητικά αποτελεί μια εναλλακτική λύση. Το τρανεξαμικό οξύ αποτελεί συνθετικό ανάλογο του αμινοξέος της λυσίνης που λειτουργεί ως αναστολέας ινοδόλυσης. Σκοπός της κλινικής αυτής μελέτης είναι η αξιολόγηση της συνδυασμένης ενδοφλέβιας και ενδοαρθρικής έγχυσης τρανεξαμικού οξέος σε ασθενείς που υποβλήθηκαν σε ολική αρthroπλαστική γόνατος και ο βαθμός ελάττωσης της ανάγκης μετάγγισης αίματος.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: ολική αρthroπλαστική γόνατος, μετάγγιση αίματος τρανεξαμικό οξύ

Slipped Capital Femoral Epiphysis: Surgical Techniques, Complications, Special Topics

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ABSTRACT

Several types of implants have been used for the treatment of SCFE. Apart from the non specific implants, such as pins or cannulated screws, other specific implants for SCFE have been manufactured. Most of these specific implants (telescopic screw, pinscrew, Hansson screw etc) efficiently prevent slip progression while preserving bone growth. Thus head and neck growth and remodeling is maintained, resulting in a lower slip angle and increased head neck offset. Femoroacetabular impingement is the most frequent complication of SCFE, that is seen even in mild slips. Its impact on the acetabulum depends on the severity but also on the chronicity of the slip. Avascular necrosis of the femoral head is the most devastating complication of SCFE leading to early total hip replacement. A rare but catastrophic complication is chondrolysis, causing a substantial articular cartilage loss. Other complications are implant related, including implant failure such as bending, migration and loosening. Prophylactic stabilization of the asymptomatic contralateral hip remains controversial. SCFE still remains a disease characterized by a high incidence of delayed diagnosis and many studies have dealt with the incidence of silent, asymptomatic and subclinical SCFE. There is still no consensus about the removal of the implants in the absence of implant-related symptoms. Lately, there is increasing interest on the role of arthroscopically assisted osteochondroplasty for the prevention and early treatment of FAI.

KEY WORDS: SCFE, surgical techniques, complications

1. Implants used for slip stabilization

Several types of implants are available for the treatment of SCFE: cannulated screws, pins and implants especially designed for SCFE treatment, such as the telescopic screw, the pinscrew or the Hansson screw. Common aim of these implants is to stabilize the slip, yet they do not have the same effect on the re-

maining growth of the proximal femoral physis.

In situ stabilization of the proximal femoral physis with one partially threaded cannulated screw (**Fig. 1**) is deemed the most efficient stabilization method for stable or unstable SCFE [1]. The cannulated screw is accompanied by a lower risk of implant related complications such as avascular necrosis and

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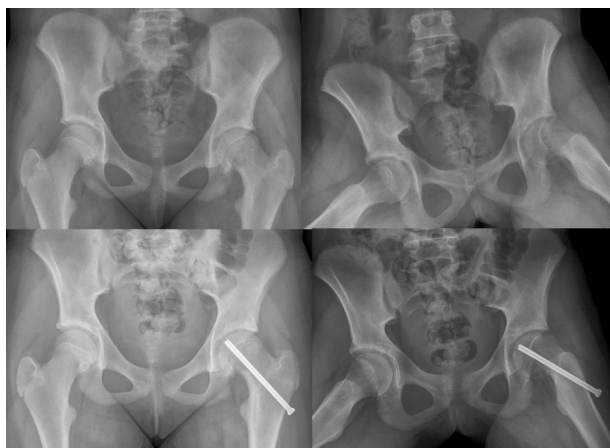


Fig. 1: *In situ stabilization of the proximal femoral physis with one 6.5mm partially threaded cannulated screw is the most accepted treatment for all types of SCFE, irrelevant of slip stability, chronicity or severity. It combines effective physis stabilization with low morbidity and a low complication rate*

chondrolysis, compared to the stabilization by multiple pins. Furthermore, if this is the surgeons intention, the screw may simultaneously compress the epiphysis on the metaphysis and thus accelerate proximal femoral physis closure [1,2,3]. The cannulated screw is inserted under intraoperative fluoroscopy, and preferably passes vertically to the center of the proximal femoral epiphysis as seen in both AP and lateral hip view ("center-center") [4], while the tip of the screw is advanced up to 2.5 mm [5] or 5 mm [6] from the subchondral bone of the femoral head. However, other studies have shown that the stability of the fixation and the incidence of complications do not differ whether the screw enters the epiphysis centrally or not [7]. The head of the screw may be in contact with the lateral cortex of the femur or protrude 2-3cm out of the lateral cortex (gliding screw technique). Stabilization is most effective when at least five steps of the screw enter the femoral head.

The insertion of a second screw [8] increases the stability of the proximal femoral physis by 66%, however other studies discourage a second screw because it does not increase the structural stability of the construct proportionally [9]. Furthermore, ad-



Fig. 2: *In situ stabilization with two 5-6mm nonthreaded pins is a safe and cheap method to treat both stable or unstable SCFE. The second pin provides rotational stability and additional stability to shear forces*

ditional implants may be associated with higher risk of complications, such as AVN, chondrolysis [9] or a subtrochanteric fracture of the femur due to weakening of the lateral femoral cortex by multiple drilling during screw placement. The strength of the stabilization increases with increasing diameter of the implant [6,10].

Safe advancement of the screw into the femoral head may be assessed by intraoperative arthrography [6]. Computer navigation may also help to reduce the distance of the screw from the subchondral bone of the epiphysis, but with increased cost and duration of the surgery [6,11].

Multiple (2-3) nonthreaded pins across the physis seem also to be a safe biomechanical alternative to the one cannulated screw (**Fig. 2**). Furthermore, multiple pins may be advantageous compared to the cannulated screw in terms of preserving the residual growth of the femoral neck [3,12,13,14].

2. Growth preserving surgical techniques

In the past, the premature closure of the proximal femoral physis was the main target of any treatment of SCFE in order to prevent slip progression [1,2,3].

However, this concept is currently being challenged. SCFE is a disease of the developing skeleton. The growth plate of the femoral head contributes significantly to the longitudinal growth of the lower limb: it provides 15% of the overall increase in length of the lower limb, at a rate estimated at about 6mm/year [15] and normally fuses at age 16-18 years. Studies of femoral neck growth and remodeling emphasize that any therapeutic intervention in SCFE should take advantage of the remaining growth of the skeleton, especially in younger patients, since a small yet significant correction of the slip angle and the head-neck offset is anticipated [16].

The surgical techniques that are used for slip stabilization, depending on their effect on the remaining growth of the physis, can be classified to those which promote premature physis closure and those which preserve residual growth.

The classic stabilization of the slip with one cannulated screw eventually compresses the physis and promotes premature fusion, which is anticipated within 6-12 months after surgery [17,18,19,20]. This technique restricts the remaining longitudinal growth of the femoral neck and eliminates the growth related decrease of the slip angle and increase of the head-neck offset. Additionally, a short femoral neck may weaken the lever arm of the hip abductors [13,18]. This is exacerbated by the continuing growth of the greater trochanter [21,22].

There are several ways to stabilize a SCFE without affecting the remaining growth, such as multiple (2-3) nonthreaded pins and the classic cannulated screw inserted with a technique that allows physeal growth (gliding screw, Gleitschraube). Especially designed screws, like the telescopic screw, the pinscrew and the Hansson pin (hook pin) are also available in order to stabilize the physis without accelerating its fusion.

Two nonthreaded pins (3-3,5mm) that traverse the physis are sufficient to stabilize the slip without promoting early closure of the proximal growth cartilage compared to the traditional cannulated screw technique [3,12,13]. The pins are inserted percutaneously under image intensification. The patient is placed either on a traction or on a regular surgical table.

The gliding screw (Gleitschraube): The classic cannulated screw may be placed in a way that stabilizes the slip without compressing the femoral neck physis. The thread of the screw is fully contained in the capital epiphysis but a screw with a relative longer shaft is selected, so that (depending on the child's age, for a presumed residual growth of 2-3 years) 1.5-3 cm of the screw protrude out of the lateral femoral cortex [5,19,24,25]. With ongoing femoral neck growth, the femoral head pulls the screw along the femoral neck until the screw head reaches the lateral femoral cortex, thus preventing further longitudinal growth of the femoral neck. If further growth is anticipated, the screw may be replaced by a longer one that protrudes out of the lateral femoral cortex too.

After stabilization with a gliding screw or with stainless steel non-threaded pins, the growth cartilage closes at about 31-37 months [5,18,23], both for the slipped and for the contralateral healthy hip [23]. Furthermore, there is no significant difference in the acetabulotrochanteric distance between the painful and the prophylactically stabilized hips [18]. Some authors showed that non-compressive stabilization (Knowless pins, Hansson pin) of the primary affected and the healthy contralateral hip leads also to simultaneous closure of the neck physis of both hips (about 17 months), while in hips that were not pinned (obviously healthy contralaterals, not clearly stated) the growth cartilage fused at about 2.5 years [25], implying some interference of implant placement with residual growth of the hip. Growth is more pronounced on the contralateral hip [18,23,26], implying that some damage on the slipped physis may be irreversible. A similar gliding mechanism, that allows further longitudinal neck growth, is provided by the Hansson pin [26].

Stabilization of the epiphysis by means of the Pinscrew [13]: the thread of the screw is located at the base of the screw and is anchored at the lateral cortex of the proximal femur, while the body of the screw is smooth and enters the femoral head, to approximately 2 mm from the subchondral bone. During femoral neck growth the capital femoral epiphysis slides along the screw. Femoral neck growth after Pinscrew fixation may eventually lead to: a) a

higher head-neck offset of the SCFE hip compared to the preoperative head-neck offset (but usually lower than the head-neck offset of the contralateral hip that has been prophylactically stabilized by the same technique), b) increased neck length (reduced compared to the length of the contralateral hip) and c) increased neck thickness (greater than the contralateral hip). The changes of the affected hip in relation to the healthy contralateral hip indicate that the growth cartilage of the SCFE hips is either primarily deficient or is irreparably damaged by the slip or by the surgical technique. Therefore, the implant that is used to stabilize the slip should have as little deleterious effect as possible on the residual growth of the physis. The Pinscrew is also effective for the treatment of unstable slips [13], indicating that growth preserving stabilization techniques are suitable for both stable and unstable slips.

The telescopic screw (Dynamische Epiphysaere Telescopschraube) is another method to stabilize the capital femoral epiphysis without promoting early physeal closure. This screw consists of two tubular parts. The one part (epiphyseal part, of smaller diameter) has a distal thread, which is anchored completely into the epiphysis. The other part of the screw (metaphyseal, of greater diameter) is proximally threaded and is anchored to the lateral cortex and the base of the femoral neck. The epiphyseal part is contained in the metaphyseal part. As the femoral neck grows, the epiphyseal part of the screw is pulled by the epiphysis and slides out of the metaphyseal part of the screw, which is firmly located at the femoral neck metaphysis. The whole construct resembles to a telescope, hence the name of this screw. The use of the telescopic screw in mild and moderate slips has led to a reduction of the slip angle by about 11° and of the α -angle by 30°. Sixty per cent of the correction was achieved within the first year of stabilization, emphasizing the importance of early diagnosis in order to maximize the benefits of bone growth and remodeling [27]. In unstable slips, the insertion of an additional nonthreaded pin across the physis is recommended in order to ensure rotational stability [27]. A biomechanical study showed that in terms of stability there was no

difference between the telescopic screw and the classic single cannulated screw, although maximal stability was observed by placing three 2mm Kirschner wires across the physis [3].

It seems that the slipped physis takes some time to resume the normal growth rate, which is probably faster in younger patients. After Hannson pin insertion (gliding pin, growth preserving), the affected hip grows initially in a caudal direction, probably due to inherent disturbance of the growth cartilage but also due to inadequate stabilization. After this initial period, growth continues in the normal direction, medially and cranially, resembling to the growth of the prophylactically stabilized hip. This explains the slightly shorter limb on the SCFE side in these patients [26].

3. Complications of SCFE

3.a. *Avascular necrosis of femoral head:*

Avascular necrosis of the femoral head (AVN) is the most devastating complication of SCFE [2,28,29]. AVN is mostly anticipated after unstable slips [28,30], complicating 24%-47% [28,31] of the cases. AVN onset is rapid, within the first year after the slip [29] and is usually located at the anterosuperior part of the femoral head, while the posteroinferior part of the epiphysis is usually spared, even in advanced stages of the disease [32].

AVN leads SCFE patients to total hip replacement within 10 years, as opposed to patients with postslip degenerative arthritis, who will undergo total hip replacement approximately 23 years after the slip [33]. A study of SCFE patients, who eventually underwent total hip replacement, showed that AVN is a more frequent cause of total hip replacement, compared to postslip femoroacetabular impingement [33].

Risk factors for AVN are: unstable SCFE, extreme displacement of unstable SCFE, a young patient with unstable SCFE [30,20], overreduction or anatomic reduction of unstable SCFE, placement of a screw or pin at the posterosuperior quadrant of the capital femoral epiphysis, injury of the femoral neck vessels due to extreme posterior placement of the implant in an attempt to aim the center of the femoral

head [34], an attempt to reduce an acute on chronic SCFE [17,21,25,35] and intra-articular osteotomies of the femoral neck [2,36].

The pathology of the impaired vascular supply of the femoral head after unstable SCFE varies. The nutrient vessels of the capital femoral epiphysis may be ruptured, twisted or obstructed either mechanically or functionally, due to a high intraarticular pressure caused by the intraarticular hematoma [37]. Closed reduction manoeuvres may dramatically increase the intra-articular pressure of the hip up to levels that exceed the pressure of a compartment syndrome and are therefore also suggested to predispose to AVN [29,37]. Since all unstable slips present pathology of chronic disease (new bone deposition at the posteroinferior neck metaphysis), any attempt to reduce the femoral head, whether open or closed, should stop at this point of chronicity and should not pass beyond it, towards anatomic reduction, otherwise the vessels of the femoral head will be compressed against this newly formed bone (callus) or may be tensed [38] and subsequently obstructed. Anatomic reduction of the capital femoral epiphysis without jeopardizing blood flow is reasonable only after removal of the posteroinferior neck callus and after femoral neck shortening by means of a modified Dunn procedure [20,39,40].

Bone scintigraphy before unstable SCFE treatment is prognostic for subsequent AVN development: cold bone scans are almost exclusively observed in unstable slips and are associated with AVN in 80-100% of the cases [36,41].

3.b. Chondrolysis

Hip pain due to a SCFE resolves almost immediately after slip stabilization. Persisting pain and stiffness of the hip after surgery may be due to ongoing articular cartilage damage of the hip joint, known as chondrolysis. Pain may be located at the hip joint or it may be reflected on the ipsilateral anterior thigh or knee. Internal rotation is further restricted and the limp of the patient is getting worse [2,20]. The diagnosis is confirmed radiologically by the loss of more than 50% of the intraarticular height compared to the healthy contralateral hip, or in case of bilateral dis-

ease, if the joint space is less than 3mm [20]. The incidence of chondrolysis is 5-7%. Its cause has not been clearly identified. Autoimmune and trophic factors, permanent intraarticular protrusion of the stabilizing implant, prolonged hip spica immobilization, severe SCFE, obesity, delayed treatment, and subtrochanteric osteotomy before physeal closure [2,20] are factors suspected to underlie chondrolysis. Transient intraoperative implant penetration into the hip joint during SCFE stabilization does not seem to be associated with chondrolysis [20,42]. The treatment of chondrolysis involves revision of the protruding implant, physiotherapy and analgesics. The overall prognosis of chondrolysis is better than that of AVN. Restoration of the joint space within 10 months is anticipated, however residual hip stiffness may persist [20].

3.c. Femoroacetabular Impingement and early onset Hip Osteoarthritis

Femoroacetabular impingement (FAI) is the most frequent complication of SCFE. Practically, all stable SCFE hips which were pinned *in situ*, even those with mild slips, are candidates for FAI development that almost always will result in osteoarthritic lesions, which may be severe or only subtle and subclinical [43,44,45,46,47,48,49]. FAI could actually be deemed not a complication, but the end point of the natural history of SCFE whether untreated or after *in situ* stabilization. After this point secondary disease and reconstruction surgery of the hip is highly anticipated.

FAI occurs during flexion and internal rotation of the SCFE hip, when the deformed femoral neck (pistol-grip deformity) impacts against the acetabular labrum and the acetabular articular cartilage. Patients with SCFE typically describe pain relief after *in situ* hip stabilization for over a period of months (6-48 months) [45] or years (6.1-20 years) [50,51]. After this time symptoms of FAI emerge, indicating permanent labral and/or articular cartilage damage [45].

In mild and moderate slips, the deformed femoral neck enters the joint resulting in abrasion of the anterosuperior labrum and the articular cartilage of the acetabulum (cam type or inclusion type femo-

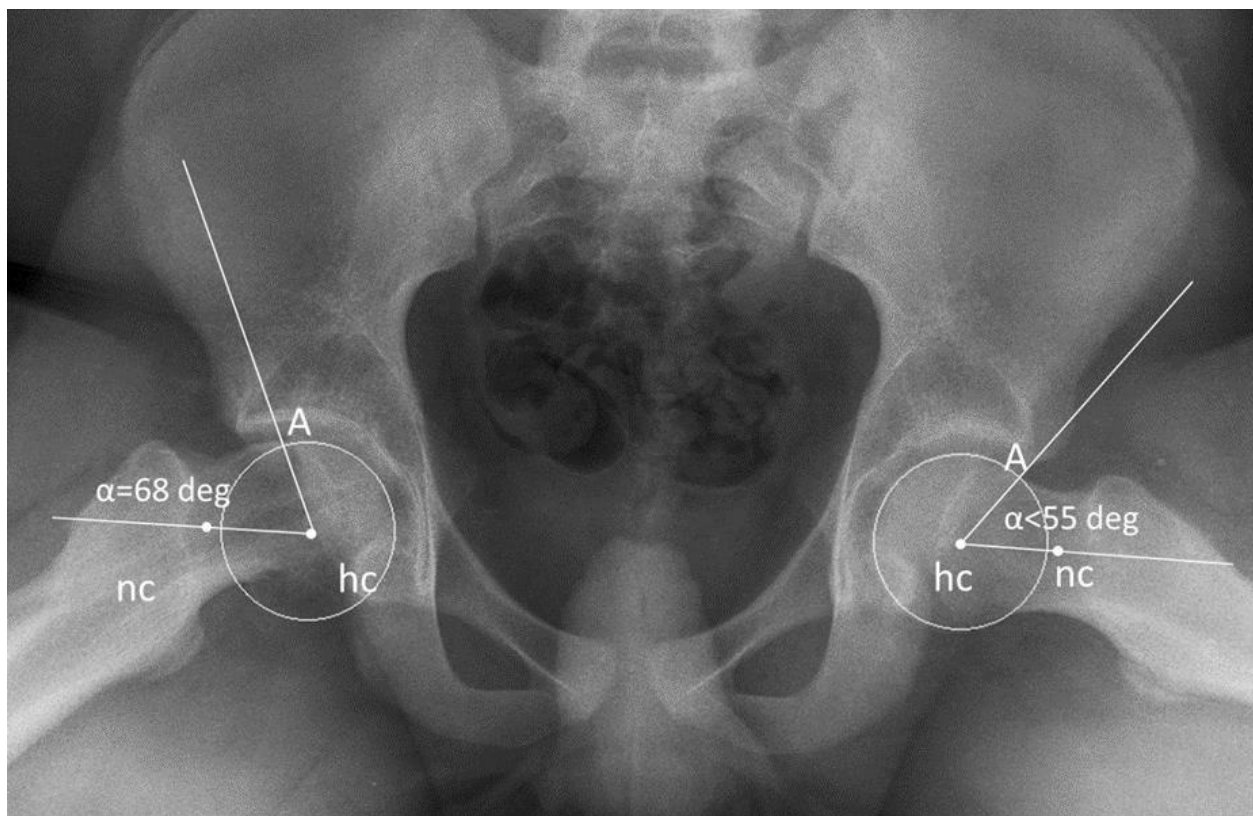


Fig. 3: The alpha angle [54] is measured on the frog lateral pelvis view. It is formed between the line hc-nc (connects the center of the femoral head -hc- with the center of the narrowest point of the femoral neck -nc) and the line hc-A (A is the point where the continuation of the femoral neck intersects with the contour of the femoral head). An alpha angle $\geq 55^\circ$ is the lower limit above which femoroacetabular impingement occurs. Left hip: $\alpha = 52^\circ$, asymptomatic, Right hip: $\alpha = 68^\circ$, symptomatic FAI

roacetabular impingement) [52]. In severe slips, the deformed femoral neck can no longer enter the acetabulum, but it strikes the rim of the acetabulum (pincer type, impaction type impingement) [52]. Intra-articular lesions that are observed in severe slips, are considered the result of impaction type impingement that occurred at the early stages of the slip [53].

Depending on its severity, FAI is heralded by pain and restriction of flexion, abduction and internal rotation of the hip. The FADIR sign is positive [51] (exacerbation of pain with flexion, adduction and internal rotation of the affected hip). Any SCFE hip with limited internal rotation ($<10^\circ$) in 90° of flexion or inability of flexion $>90^\circ$ is suspected for FAI [46,47,54]. Characteristic of FAI is the Drehman sign, that is, the progressive mandatory external rotation of the thigh

when the patient tries to flex the hip. This is due to an attempt of the hip to overcome the impact of the deformed anterosuperior femoral neck on the anterosuperior acetabulum. Sitting on a chair may be problematic in severe cases.

The risk of FAI in SCFE increases with slip severity: FAI will present 100% of the patients with a severe slip, 50% of the patient with a moderate slip and 33% of the patients with a mild slip [55]. Mild slips are not free of risk for FAI [20,39,45,53,55,56]. However, many authors report that symptoms of FAI appear at a slip angle $>30^\circ$ [55,57] and exacerbate further depending on the concomitant decrease of the head-neck offset [57]. Eventually, regardless of slip severity, 80-90% of the treated slips will present labral and acetabular cartilage lesions [1,45]. The

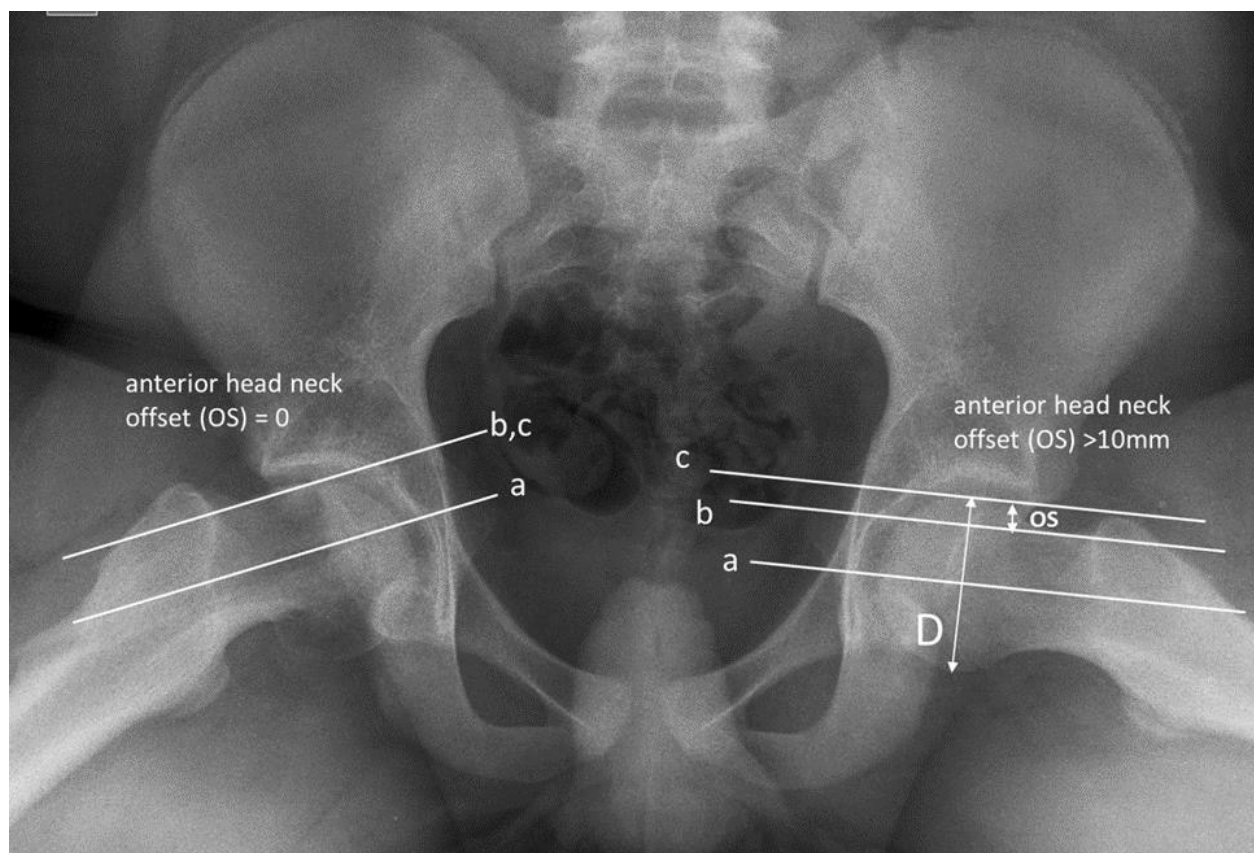


Fig. 4: the Anterior Head Neck Offset (OS) and the anterior Head Neck Offset Ratio (HNOR) are calculated on the frog lateral pelvis view. A line (a) is drawn across the axis of the femoral neck. A second line (b) is drawn parallel to (a) at the level of the anterior contour of the femoral neck. A third line (c) parallel to (a) is drawn across the upper border of the femoral head. The widest diameter of the femoral head is measured as D. The distance between the lines b and c is defined as the Anterior Head Neck Offset (OS) and is normally ≥ 10 mm. The ratio OS/D is deemed the anterior Head Neck Offset Ratio (HNOR), that in normal hips exceeds 0.15. Left hip: normal OS and HNOR, asymptomatic. Right hip: zero (!) OS - HNOR, symptomatic FAI

labral lesions appear soon (within 6-12 months) after slip onset, are located between the 10th and the 3rd hour of the acetabulum and are observed even in mild slips [39,45,49,58,59]. Later on (within about 3 years) acetabular cartilage defects (Outerbridge 3 and 4) appear [45,58]. The labral and joint cartilage damage may be subclinical for a long period of time, but once symptomatic it may eventually lead to early reconstructive hip surgery [59].

The radiologic diagnosis of FAI is made on the frog lateral pelvis view [60]: an alpha angle $>55^\circ$ [54] (Fig. 3), an anterior head-neck offset ratio (HNOR:

neck-head offset divided by the femoral head width) <0.15 [60] and an anterior femoral head - neck offset <10 mm (OS) are signs indicating FAI [61] (Fig. 4). Some authors suggest a high risk of FAI when the alpha angle on the cross table lateral hip projection is $>70^\circ$ [62]. However, the original description of the alpha angle was based on MRI scans [54]. Other projections that are useful for the radiologic assessment of FAI associated femoral neck deformity are the 45° Dunn view (45° hip flexion, neutral rotation, 20° abduction) because this view portrays the maximal femoral head asphericity [51], and the

TABLE 1. *SCFE is a cause of early onset hip osteoarthritis and total hip replacement (THR)***1. Patients treated for SCFE in adolescence**

Abraham 2007 [67]	SCFE patients undergo THR 11 years earlier compared to patients with primary hip osteoarthritis
Wensaas 2011 [43]	<ul style="list-style-type: none"> • Mean age at THR <ul style="list-style-type: none"> - of SCFE patients: 48 years - of primary hip osteoarthritis patients: 69 years. • Patients with a history of SCFE in adolescence will receive a THR: <ul style="list-style-type: none"> - 9% in 30 years - 23% in 40 years
Larson 2012 [56]	5% of SCFE patients will have a THR within 20 years from SCFE diagnosis

2. Radiologic studies in patients with hip osteoarthritis

Murray 1965 [68]	<ul style="list-style-type: none"> • SCFE is the underlying cause in 4.1-6.5% of cases of hip osteoarthritis • 39.5% of patients with hip osteoarthritis without a history of hip symptoms in adolescence present a pistol grip deformity of the femoral neck (described by the author as "tilt deformity of femoral head"). These cases may be attributed to a silent, hence undiagnosed, SCFE
Clohisy 2011 [69]	<ul style="list-style-type: none"> • SCFE is the cause of hip osteoarthritis in 2.9% of patients that undergo a THR before the age of 50 years. According to the authors, SCFE represents a distinct severe cause of FAI. • Cam type FAI is the cause of hip osteoarthritis in 9.3% of patients that had a THR before the age of 50 years
Murgier 2013 [48]	<ul style="list-style-type: none"> • Age at THR: 56.2 years (SCFE patients) vs 66 years (primary hip osteoarthritis patients) • radiologic signs that suggest a SCFE history are present in 24.7% of all THR patients and in 35.7% of THR patients younger than 60 years.

false profile hip view (patient standing, pelvis angled 65° to the cassette, foot parallel to the cassette) [62]. Therefore, the comparison of the alpha angle of the SCFE hip with that of the opposite asymptomatic hip seems reasonable in order to diagnose a symptomatic FAI causing neck deformity. The head-neck offset affects hip mobility independently from the slip angle. A decreased head-neck offset may restrict hip mobility of a moderate slip to that observed in case of a severe slip [57].

The incidence and severity of FAI induced labral and articular cartilage damage of the acetabulum increase with slip chronicity [39] and slip severity [47]. Interestingly, slips that were deemed unstable during surgical hip dislocation presented less labral and acetabular cartilage damage compared to chronic stable hips, probably because the dramatic clinical presentation of instability forces the patient to seek early medical care [39]. This explains why *in situ* stabilization yields better long term results in patients

with acute on chronic slips compared with patients who suffer chronic slips of the same severity [63].

According to some authors, the correlation of radiologic signs of SCFE (slip angle, alpha angle) with the clinical presentation of FAI is not statistically significant [51]. This is because the clinical (symptomatic) FAI is multifactorial and depends on the patient's occupation and level of physical activity, and on other anatomic factors of the hip as well, such as the acetabular depth (coxa profunda), the femoral neck version [51], the acetabular version (retroversion results in mixed type cam and pincer FAI) [20,51,64] and an anterior and lateral Center-Edge Angle of the acetabulum >35° [46,64]. These factors multiply the damaging effect of the abnormal postslip femoral neck on the acetabulum.

The end result of FAI is secondary hip osteoarthritis and a total hip replacement at a younger age, compared to the general population. Osteoarthritic lesions of the hip are extremely common in patients

with SCFE (Haeggglund 1987: 24% of SCFE hips were osteoarthritic after 28 years follow up) [21] and are observed in all types of slip severity [56]. Furthermore, SCFE is the most frequent (35.7%) cause of hip osteoarthritis in patients younger than 60 years of age [48].

The incidence of total hip replacement in SCFE patients has not been clearly elucidated, because all published studies are retrospective. It appears, however, that SCFE patients will undergo a total hip replacement at least 10 years earlier than patients with idiopathic hip osteoarthritis (**table 1**).

3.d. Implant related Complications

In addition to complications inherent to SCFE (AVN, chondrolysis, FAI), there are complications related to the surgical technique, the type of the implant that is used to stabilize the slip and the impact of the implant on the residual growth of the femoral neck physis.

Thin pins may migrate, loosen or bend under the patient's weight and may lead to slip progress. In the treatment of severe slips, aiming the center of the capital femoral epiphysis may result in extreme posterior placement of the implant (pin, screw) into the femoral neck. At this position the implant may injure the nutrient vessels of the epiphysis, either at their course in the posterosuperior (lateral) retinaculum [65], if the implant exits the posterosuperior neck cortex [34], or at the posterosuperior quadrant of the epiphysis, where the nutrient vessels enter the capital femoral epiphysis [2,42,66].

Implants that protrude into the hip joint will inevitably result in hip chondrolysis, while temporary intraoperative joint penetration by the implant does not seem to increase the risk of chondrolysis [20,42].

Occasionally, the remaining femoral neck growth may cause the epiphysis to "grow out" of a non-threaded pin. In this case, the epiphysis disengages from the implant and slips further on the femoral neck (lost epiphyseal grip due to growth) [21]. Cyclic loading on the free end of a pin that protrudes out of the lateral femoral cortex may cause this pin to loosen and migrate (windshield wiper loosening, lost epiphyseal grip due to sliding) [21,23].

Multiple drilling of the femur in order to obtain a perfect pin/screw insertion into the femoral neck and head may significantly weaken the lateral femoral cortex and result in a fracture of the femur at the point of screw insertion [23,34]. The same can be observed after physeal fusion, if excess bone is removed from the femur in an attempt to expose and remove deep buried implants.

An entry point of the implant at or below the lesser trochanter should be avoided, since it may predispose to a subtrochanteric fracture [42]. The risk of complications rises with the number of pins or screws that are used.

Considering the above, one screw fixation seems to be the optimal method to treat SCFE, because it combines stability with a low risk for implant related complications [1,66,70]. The surgeon should insert the implant above the level of the lesser trochanter and avoid multiple drilling of the lateral cortex [1,66].

In addition to the Cam-type FAI, hip flexion may occasionally cause the screw head to impinge against the acetabulum. This is observed when the entry point of the screw is placed on the anterior metaphysis, medial to the intertrochanteric line, in an attempt to insert the screw vertically through the center of the epiphysis [17]. This risk can be avoided if the screw entry is lateral to the intertrochanteric line. The oblique course of the screw does not seem to harm the stability of the fixation [71,72].

4. Special topics about SCFE

4.a. Bilateral disease - Prophylactic fixation of the Contralateral Hip?

Klein estimated the frequency of bilateral hip involvement in SCFE up to 40% of the patients [73]. However, the incidence of contralateral disease seems to be much higher [42,74,75,76]. One may consider that a frequency of bilateral hip involvement of about 50% within 2 years of the first hip disease is a reliable estimate that complies with most reports. The risk of bilateral disease is much higher in obese patients or in patients with endocrine disorders [22], where the contralateral hip may be involved in up to 100% of patients [77]. It has been calculated that

the risk of contralateral disease of a patient with one SCFE hip is 2,335 times higher than the risk of the general population to suffer the first SCFE [78]. The most extreme view was recently stated by Billing, who suggested that theoretically all slips are bilateral, just in some patients the fusion of the contralateral hip physis prevents the slip angle from exceeding 13°, that is deemed the upper normal limit [79].

The contralateral hip may present SCFE either simultaneously with the first hip (8-27%) [75], or later, usually within 3-5 months after the first hip disease (19-40%) [23,75]. However, not infrequently, the contralateral slip is first diagnosed in adulthood, either incidentally (e.g. pelvis x-ray after an accident) or because the patient complains of a nontraumatic painful hip. This is due to either a missed diagnosis during adolescence or to a subclinical contralateral disease during adolescence (asymptomatic or silent slip). Indeed, most contralateral slips (41-92%) [74,75,80] are asymptomatic, and when diagnosed in adulthood they often (29%) present secondary osteoarthritic lesions [21].

It is obvious that the contralateral hip should always be stabilized if symptomatic. It should also receive prophylactic stabilization if it is asymptomatic but with radiologic evidence of an established slip or a preslip. However, the question is whether the asymptomatic and radiologically normal contralateral hip should undergo prophylactic fixation in order to prevent future SCFE. Obesity and underlying hormonal disorder are certainly indicative of prophylactic stabilization of an asymptomatic contralateral hip. However, there is no consensus among the authors.

The opponents of prophylactic stabilization of an asymptomatic contralateral hip argue that prophylactic stabilization of the contralateral hip bears complications too, although not as frequent as in case of therapeutic slip stabilization [81]. Such complications are inflammation [82], AVN [20,33,42,83] and implant-related fracture [42]. Other authors question the increased risk of secondary osteoarthritis of the contralateral hip [43,84], despite the increased alpha angle observed on the contralateral hip of patients with SCFE [84]. Others advocate that the pre-

ventive contralateral physis stabilization represents unnecessary surgery in 59% [80] to 81% [78] of cases, because the contralateral slip is usually a mild (73-78%) [78,85] acute SCFE (the first hip is usually a chronic slip [85]), that is promptly diagnosed (alert patient and physician) and treated. On the other hand, it is questionable if prophylactic fixation of the asymptomatic contralateral hip may spare this hip from the development of a pistol grip deformity or a retroverted femoral head, which are considered as the mildest forms of a silent SCFE. Furthermore, these mild deformities are frequently found in asymptomatic adults and it is not evident that they predispose to hip osteoarthritis [78].

The advocates of prophylactic stabilization of the healthy contralateral hip state that the morbidity and the complications of prophylactic fixation are minor compared to those observed with therapeutic intervention for the established slip [27,40,75,86,87,88]. Furthermore, prophylactic fixation spares the contralateral hip from a silent slip and the prophylactically fixed hip rarely presents radiographic evidence of Cam type FAI [51,76]. Hansson suggests that the contralateral hip should receive growth preserving prophylactic treatment only in case of endocrine disorder, obesity, a delay in the diagnosis of the first hip or if geographical or social factors will omit prompt medical care to the patient [22].

Preventive stabilization of the contralateral hip bears some controversy in regard to the remaining growth of the hip. Prophylactic stabilization of the contralateral hip does not seem to accelerate physal closure relative to the primary SCFE hip, provided that a growth preserving technique is applied [18,23,25,26]. Growth arrest promoting techniques, such as the classic (compressive) insertion of a cannulated screw is no longer favored compared with multiple K-wire stabilization [14]. Other surgeons abandon K-wires for prophylactic pinning in order to avoid disengagement of the capital femoral epiphysis out of the stabilizing implant by the growing femoral neck [22]. However, it is reasonable to fix the contralateral hip with the same implant and technique as the primary hip in order to affect the residual growth of both hips symmetrically. This implant

should not promote early physeal closure, especially in younger children, that are prone to present bilateral disease.

Between those extremes is the attempt to identify signs that may predict increased risk for future contralateral hip disease, in order to select patients with unilateral SCFE for targeted preventive stabilization of the contralateral hip.

The posterior sloping angle of the femoral neck physis, i.e. the angle formed by the physis (not the epiphysis! – slip angle) and a line vertical on the femoral neck-shaft axis as seen on the frog lateral pelvic projection has been suggested to predict increased risk for future SCFE of the contralateral hip [89]. This angle depicts the orientation of the physis and seems to be a significant anatomic difference between SCFE and normal hips [89]. A posterior sloping angle greater than 12°-15° [20,90] entails increased risk of slippage and is indicative for preventive stabilization [20], while a slope angle of >19° is observed in symptomatic slippage and the corresponding hips should be stabilized [91].

The modified Oxford score estimates the slip risk of the contralateral hip by assessing five radiologic parameters that are visible in the pelvis view: The iliac crest, the triradiate cartilage, the capital femoral epiphysis, the trochanter major and the trochanter minor are each scored in one of three stages of maturation. Younger patients have lower scores and have a greater risk for contralateral hip disease. A total score of 16.17 or 18 has a 96% positive predictive value and 92% negative predictive value and is probably the most reliable predictor of a future contralateral slip [92].

The maturation of the triradiate cartilage appears to be a reliable prognostic factor *per se* for an increased slip risk, yet not as effective as the modified Oxford score. An open triradiate cartilage (Grade 1 in the scoring system) implies a 89% probability for a contralateral slip [92].

The alpha angle is also a useful predictor of a contralateral SCFE: an alpha angle >50.5° is associated with increased risk of contralateral hip involvement and could be used as a threshold for prophylactic stabilization of the contralateral asymptomatic hip [93].

Other factors that favor prophylactic stabilization of the contralateral hip are: obesity (BMI >95th, >35kg/m²), young age (girls <10 years, boys <12 years), female gender, endocrine disorders [20,90,94,95,96,97].

4.b. Subclinical – Silent – Asymptomatic SCFE?

Hip morphology suggesting an underlying SCFE is a frequent finding in the adult population, ranging from 6.6% in a healthy cohort of young adults [100] to 24.7% in patients who had a total hip replacement [48]. Similar morphology was found in 8% of bone samples [98]. Moreover, most contralateral slips are first diagnosed in adulthood without a positive history for hip disease [74,75,80].

Compared with the rarity of SCFE in adolescence, this increased SCFE morphology in end-stage osteoarthritis of the hip strongly suggests the existence of a subclinical (silent, asymptomatic) slip of the capital femoral epiphysis, that stops with physis fusion. Some of these silent slips will become symptomatic in the adult life. A Southwick angle >13° at physeal closure of a hip without a SCFE history during adolescence sets the diagnosis of a silent SCFE [79]. Nevertheless, the ratio between the symptomatic (pain, limp) diagnosed SCFE, the symptomatic missed (nondiagnosed) SCFE and the asymptomatic (silent, subclinical) SCFE is unknown.

4.c. Post-slip and Slip-like Femoral Neck Deformity

More than 50 years ago, it has been suggested that a mild deformity of the proximal femur, that resembles to the pistol grip deformity observed in SCFE might be the cause of 39.5% of cases of hip osteoarthritis, which were originally classified as idiopathic (primary or of unknown etiology, in patients without history of hip symptoms in the adolescence [68]). This deformity was originally described by Murray (1965) as the “tilt deformity of the femoral head”. It is observed mostly in men and becomes symptomatic before the onset of radiological signs of hip osteoarthritis [68].

The question is to what extent the femoral head-neck deformity that leads to a Cam-type FAI is the result of a pre-existing SCFE. It is estimated that slip-

like (of unknown etiology, no SCFE history in adolescence) or post-slip (after *in situ* pinning for SCFE in adolescence) morphology (positive fovea sign: the neck axis does not pass through the fovea capitis; tilt angle: the angle between the perpendicular to the line joining the edges of the capital femoral epiphysis and the axis of the femoral neck $>4^\circ$) account for 12% and for 3% of all cam type FAIs respectively [99].

It seems that post-slip hip deformity that leads to hip osteoarthritis and total hip replacement is less frequent compared to the slip-like deformity of the femoral neck (**table 1**). This is due to the fact that the suggestion of an underlying SCFE in the adult hip is based on a different methodology (pistol grip deformity, fovea sign, tilt angle etc), which is not applied to the adolescent hip (Klein line etc). Therefore, the prevalence of post-slip and slip-like deformity in the adult population are not comparable and there is an obvious risk to overdiagnose an underlying SCFE in the adult hip. However, the increased SCFE morphology in end-stage osteoarthritis of the hip may to some extent reflect the high incidence of subclinical or undiagnosed SCFEs that were never treated in the past and that will become symptomatic in the adult life [98,100].

4.d. Delayed diagnosis or missed diagnosis?

An average delay of 14.6 months to diagnose and hence to treat SCFE has been reported since almost a century ago [35]. To date, progress towards a prompt diagnosis has not been spectacular, as recent studies report an average delay in the diagnosis of SCFE of about 5-7 months [43,73,101,102,103] with 1,186 days being the most extreme reported delay [104].

There are various explanations for this delay. Some factors are related to the patient, such as the subjective perception of hip pain and limp by the patient or the educational and social status of the family. Other causes of a delayed diagnosis are the availability and accessibility of any kind of Health Service. However, in about the half cases, the cause of late diagnosis is the physician himself [105,106], usually a non-orthopedic. In this case, the delayed

diagnosis is a diagnosis missed by the health professional [103,106].

A stable, slowly progressing slip, which is accompanied by relatively mild symptoms, may be underestimated by the patient and the doctor as well. History of pain may obscure the diagnosis: only half of cases complain of hip pain [2,17,101]. In the remaining cases, patients report knee pain (26%), thigh pain (16%), or a painless limp (8%) [101]. It is not uncommon for the doctor to be misled by the referred pain on the thigh or the knee and to seek radiological control of the respective anatomic regions. Even if the clinical examination indicates hip pathology, the classic anteroposterior pelvis view has low sensitivity for a SCFE diagnosis. The frog lateral (Lauenstein) pelvis view is the most appropriate examination for this purpose [107,108], yet this projection is ignored and not even requested by many physicians, or it is usually requested at a subsequent visit of the complaining patient [106,109]. Patients examined by specialized orthopedic surgeons have the shortest delay in diagnosis compared with other doctors involved in primary health care [103]. This should raise attention to all non-orthopedic health professionals (primary care, trainees), who will most likely be the first to examine the adolescent with a non-traumatic limp [104].

The duration of the symptoms until hip stabilization, in other words the length of the delay in diagnosis and treatment, is directly related to the severity of the slip [43]. A greater delay of the diagnosis is associated with higher slip severity [17,21,43,100,110,111] and worse long term results after treatment [101]. For each month of delay of diagnosis the severity of the slip increases by one level [43,102].

Considering that mild SCFEs have excellent prognosis in 94-96% of cases [112], that femoral neck residual growth and remodeling will correct the slip angle about 10° - 15° and the alpha angle about 10° - 30° and that FAI is observed with a slip angle $>30^\circ$ [55,57] and an alpha angle $>55^\circ$ [54], it is concluded that a delayed diagnosis and treatment of SCFE deprives the hip of the potential to regress to a less severe deformity and thus to avoid FAI and early onset secondary

osteoarthritis. Given that in-situ stabilization is the universally accepted treatment for all SCFEs, it appears that early diagnosis is the most important factor in order to obtain satisfactory long-term results with this treatment [73,109]. Therefore, SCFE should be a key component of the differential diagnosis of every non-traumatic limp of the adolescent.

A delayed diagnosis refers almost always to stable slips. It is extremely uncommon for an unstable slip to skip immediate diagnosis and treatment, because the dramatic clinical presentation urges the patient to seek medical help. However, if an unstable slip is left untreated, it seems that after 2-3 weeks the hip pain moderates but always persists. Within months the hip is stiff in flexion, adduction and external rotation [2]. Osteoarthritis is evident on x-ray [2].

4.e. Growth and Remodeling in SCFE

4.e.1. Limb Length Discrepancy in SCFE

Postslip Limb Length Discrepancy (LLD) is always due to a -ipsilateral to the SCFE hip- shorter lower limb [51]. In a retrospective study of patients with SCFE, who did not receive surgical treatment, the ipsilateral limb was 2-5cm shorter and the ipsilateral thigh circumference was 2-7cm thinner compared to the contralateral [113]. A retrospective study of patients operated for SCFE showed that the operated lower limb was only 0.5-0.8 cm shorter than the contralateral in almost all cases [21].

There are two types of LLD in SCFE: apparent LLD and true LLD. The true LLD is attributed to the posterior and medial epiphyseal slip and the subsequent proximal migration of the femoral neck. It is also secondary the potentially disturbed remaining growth of the slipped physis due to mechanical trauma or added surgical morbidity. True LLD is evident in moderate to severe slips and is on average 14-15 mm at the time of physeal closure [114,115]. The apparent shortening is slightly greater than the true shortening (~17mm). It is also observed in moderate to severe slips and is the result of the restricted abduction of the affected hip in an attempt to avoid impingement of the deformed femoral neck on the acetabulum (cam type FAI). The patient compensates the restricted abduction by ipsilateral pelvis eleva-

tion during walking [114]. Older children may present a greater LLD, probably secondary to a delayed diagnosis and hence a slip of higher severity and less remaining growth [115].

4.e.2. Bone Remodeling of the SCFE hip

Femoral neck remodeling of the SCFE hip has been described since almost a century ago [35]. This process consists of bone absorption at the anterosuperior surface of the femoral neck metaphysis and bone deposition at the posteroinferior aspect of the metaphysis. Femoral neck remodeling starts shortly after slip initiation. Callus formation at the posteroinferior neck is evident on ultrasound three weeks after slip onset and signals the transition of the acute slip to a chronic one [116].

Bone absorption at the anterosuperior metaphysis results in the formation of a hump (or bump), known as the "Herndon's hump". Bone deposition at the posteroinferior metaphysis is described on the frog lateral pelvis view as the "crow's beak" sign [73]. There is shortening and overall thickening of the femoral neck. The proximal femur assumes the "pistol grip deformity".

Femoral neck remodeling may be beneficial for the postslip anatomy of the proximal hip (**table 2**) and may prevent FAI or gait disturbance, but this potential is not unlimited. Some correction of the slip angle, the alpha angle and the head-neck offset is anticipated in relatively younger patients with mild or moderate slips, but not in severe slips [19,11]. Unfortunately, this correction will probably not compensate a slip angle of >30° [55,57]-35° [118] and thus will not be able to prevent FAI and early hip osteoarthritis. Therefore, a slip angle of 30°-35° could theoretically be the upper limit for *in situ* stabilization, while in more severe slips additional surgery (arthroscopic osteochondroplasty, open osteochondroplasty, modified Dunn procedure) should be considered in order to prevent FAI [55,118]. However, according to the same authors, the generally reported good long-term results after *in situ* stabilization of moderate slips, do not justify prophylactic surgery for FAI in moderate slips, unless the hip becomes symptomatic [118].

TABLE 2. *The effect of femoral neck remodeling on factors associated with FAI after in situ fixation of SCFE*

Jones 1990 [19]	<ul style="list-style-type: none"> • 70 hips, 7.1 years after in situ pinning, probably classic cannulated screw • remodeling occurred in 90% of patients with mild slips and 50 % with moderate slips. • 75% satisfactory remodeling if slip angle $\leq 40^\circ$ • Hip kinematics: remodeling leads to an increase of internal rotation of the hip.
Wong-Chung 1991 [125]	<ul style="list-style-type: none"> • 55 hips, in situ fixation, classic cannulated screw • Mean slip angle correction: 11.7° (6°-25°) • Compensatory (non anatomic) osteotomy should be considered 2 years after slip fixation, if remodeling is insufficient.
Belleman 1996 [25]	<ul style="list-style-type: none"> • 59 hips, Knowless pins, Hansson pins • Slip angle reduction: 13.5° on the frog lateral view, 7° on the anteroposterior pelvis view • Increased width of the neck (+2.95mm compared to contralateral) • head - neck angle: correction towards 0° (normal, optimal support of the epiphysis on the metaphysis) • excellent results in 90% of patients, except of a slight (!?) reduction of internal rotation of the hip
Kumm 2001 [23]	<ul style="list-style-type: none"> • gliding cannulated screw • 29 slips in 25 patients, • Mild slips ($<30^\circ$) • longitudinal neck growth 15-30 mm, • slip angle reduction 15%
Dawes 2011 [117]	<ul style="list-style-type: none"> • 59 hips, mild-moderate SCFE • in situ stabilization with one cannulated screw • alpha angle correction: 17.7° • Klein's line offset increase 4.8 mm
Akiyama 2013 [119]	<ul style="list-style-type: none"> • 69 hips, 56 patients, stable SCFE, in situ pinning • Mean alpha angle correction: 24.9° • Mean Head-Neck Offset Ratio (HNOR) correction: $0.086 \Rightarrow 0.135$ • Residual cam type deformity in 29.4 % of patients
Schumann 2016 [27]	<ul style="list-style-type: none"> • 19 cases, retrospective study, stable and unstable SCFEs • telescopic screw • Slip angle correction from 30.3° to 19.3° • Alpha angle correction from 91.3° to 62° • in 9 of 11 patients: correction of the neck shaft angle (varus neck due to slip) • the maximal correction was observed 6-12 months after slip stabilization
Megalooikonomos 2017 [126]	<ul style="list-style-type: none"> • mean correction of alpha angle: 13.45° • mean correction of the HNOR: $-0.030 \Rightarrow +0.039$

Growth and remodeling of the femoral neck progress as long as the physis is open and end with physis fusion [19,23]. It appears that FAI is less common in children younger than 11 years [119]. A sign indicative of the remaining growth and remodeling potential of the SCFE hip is the triradiate cartilage of the acetabulum. Fusion of the triradiate cartilage precedes femoral neck physis closure by 12 months [5]. There are three stages of maturation of the triradiate cartilage: open, intermediate open and closed triangular cartilage [120]. A wide to intermediate

open triangular cartilage implies a significant residual growth and remodeling potential of the affected hip [111] that might be effective to improve the postslip femoral neck deformity even in moderate slips [13,120]. Such patients may benefit from growth preserving slip stabilization surgery (technique, implant) [27,120].

However, the correction of the femoral neck-head relationship through bone remodeling after *in situ* slip stabilization is significantly less compared to the immense correction achieved after a modified Dunn

TABLE 3. *Current concepts for the treatment of SCFE***1. Stable SCFE****a. mild (<30°):**

1. in situ stabilization
2. ± growth preserving technique in case of open triradiate cartilage
3. ± osteochondroplasty (open, arthroscopic)

b. severe (>50°):**i. open physis:**

1. in situ stabilization
2. anatomic reduction (modified Dunn procedure)
3. ± osteochondroplasty (open, arthroscopic)

ii. closed physis (in case of FAI following primary in situ fixation)

1. subtrochanteric osteotomy Southwick, Imhauser
2. osteochondroplasty (open, arthroscopic)

c. moderate (30°-50°): treat as mild or severe SCFE!**2. Unstable SCFE:****a. Incidental reduction ± decompression of hip haematoma + in situ stabilization (AVN 0-50%)****b. Partial reduction with arthrotomy (Parsch) + pinning (AVN 5%)****c. Modified Dunn procedure (AVN 0-26%)**

procedure of the hip (alpha angle correction: 53°, slip correction: 43°) [114].

4.f. Should the implants be removed?

Implant removal after fusion of the proximal femoral physis bears some risks (34%-50%) [121,122]. A partially threaded screw may not “unscrew” or it may break. Titanium screws may bind strongly to the bone and their removal may be particularly problematic. Excess bone removal at the lateral femoral cortex in order to access an implant that is buried deep into the bone may increase the risk for a pertrochanteric fracture. Despite the general perception that the implants should be always removed because they may cause late inflammation, malignancy or make a future total hip replacement difficult, it seems that such complications lack literature support [121]. For this reason, SCFE stabilization implants should be removed only if they are deemed responsible for secondary symptoms such as tendinitis of the iliotibial band, bursitis of the greater trochanter or if the implants are loose and migrate. However, there are no clear indications to remove or not an asymptomatic implant and the surgeon should assess the risks and benefits of this additional surgery [121].

4.g. The role of hip arthroscopy in the treatment of SCFE

Arthroscopic osteochondroplasty of the femoral neck is a useful procedure in the treatment of SCFE and may be performed either simultaneously with *in situ* pinning [123] or later [59], in order to prevent or treat FAI [124].

Arthroscopic osteoplasty reduces the alpha angle by 20°-40° and increases the head-neck offset [58,59], not only in mild and moderate but also in severe slips (slip angle up to 65°) and leads to a remission of FAI related pain as well as to increased hip motion [58].

Hip function both before and after arthroscopic osteochondroplasty is inversely related to the time elapsed from slip onset (duration of slip). For this reason, neck osteochondroplasty should be performed as early as possible in order to avoid irreversible damage of the labrum and the acetabular cartilage [58]. Consequently, the question is whether mild and moderate slips should undergo early arthroscopic osteochondroplasty, or should the post-slip femoral neck deformity be addressed later, after femoral neck remodeling is complete [59]?


A shortcoming of arthroscopic osteochondroplasty is that it does not restore the normal relation between the femoral head and the load bearing surface

of the acetabular roof. The articular cartilage of the femoral head has a maximum thickness around the area of the fovea capitis, while the cartilage at the periphery of the femoral head is thinner. Femoral head retroversion seen in SCFE leads to a change of the normal load bearing surface of the femoral head. Acetabular load is transmitted through regions of the femoral head with a thinner articular cartilage. Thus, even in the absence of FAI, the femoral head cartilage may present a higher risk for early damage [67]. Therefore, anatomical femoral epiphysis reduction by means of a modified Dunn procedure (and not arthroscopic osteochondroplasty) is expected to be more effective in preventing early osteoarthritis of the SCFE hip, especially in the treatment of moderate and severe slips.

There are only a few published cases of arthroscopic subcapital osteotomy in moderate and severe stable SCFE. The technique is extremely demanding but reportedly quite effective, with a mean restoration of the slip angle of about 40° and a significant improvement of hip function. There is no need for a trochanteric osteotomy and the ligamentum teres is spared. Main disadvantage of this method is the relative short follow-up, so that safe conclusions cannot be drawn [127].

Hip arthroscopy may also be useful in the treatment of unstable slips. Reduction of the capital femoral epiphysis to the pre-slip position without tensioning the nutrient vessels has been attempted. The results are promising, yet a longer follow up of more cases are needed before this technique is adopted for the treatment of unstable slips [95].

5. Conclusion

The effectiveness of any treatment for SCFE depends on two factors: (a) early diagnosis, that results in less proximal femoral deformity and less damage to the acetabulum due to FAI, and (b) the restoration of the femoral head – neck relationship, either through growth and remodeling or by means of surgery. A SCFE of higher severity and duration is associated with more severe lesions of the labrum and the articular cartilage of the acetabulum and with more severe osteoarthritic lesions of the hip. On the other hand, *in situ* stabilization of a slipped physis is not enough to reverse the continuing damage of the acetabulum that is caused by a permanently deformed femoral neck. Table 3 summarizes current concepts on how to deal with SCFE. There is a trend towards more aggressive methods, such as hip arthroscopy and modified Dunn procedure. Prospective randomized studies will highlight the most appropriate technique. Until then, *in situ* stabilization is the safe choice for the patient and the surgeon. The prevention of child obesity is a key factor in order to reduce the incidence of SCFE. Delay in diagnosis and treatment leads to worse long term outcomes. Therefore, SCFE should be always kept in mind of the primary care provider when dealing with a limping adolescent. The frog lateral projection of the pelvis should always be requested when examining a non traumatic limping adolescent. 

Conflict of interest:

The authors declared no conflicts of interest.

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ΠΕΡΙΛΗΨΗ

Διάφοροι τύποι υλικών έχουν χρησιμοποιηθεί για την αντιμετώπιση της Επιφυσιολίσθησης της Μηριαίας Κεφαλής (ΕΜΚ). Εκτός από τα μη ειδικά υλικά, όπως οι βελόνες και οι αυλοφόρες βίδες, έχουν κατασκευαστεί επίσης ειδικά για την ΕΜΚ υλικά, όπως είναι η τηλεσκοπική βίδα, η βίδα-βελόνα, ο ήλος Hansson κτλ. Χαρακτηριστική ιδιότητα των τελευταίων είναι ότι σταθεροποιούν την ολίσθηση χωρίς να καταστέλουν το υπολειπόμενο δυναμικό ανάπτυξης της εγγύς μηριαίας επιφύσης. Η διατήρηση της ανάπτυξης, σε συνδυασμό με την ανακατασκευή του μηριαίου αυχένα, έχει ως συνέπεια τη μείωση της γωνίας ολίσθησης και την αύξηση του offset μηριαίας κεφαλής - μηριαίου αυχένα, γεγονός που αποδεικνύεται ευεργετικό ως προς την αποφυγή μηροκοτυλίας πρόσκρουσης, ιδιαίτερα σε μικρής και μέτριας βαρύτητας ολίσθησεις. Η μηροκοτυλία πρόσκρουση αποτελεί την πιο συχνή επιπλοκή της ΕΜΚ, η οποία παρατηρείται ακόμα και σε μικρής βαρύτητας ολίσθησεις. Η άσηπτη νέκρωση της μηριαίας κεφαλής αποτελεί την πιο καταστροφική επιπλοκή της ΕΜΚ και αναπόφευκτα οδηγεί σε πρόωμη ολική αντικατάσταση του πάσχοντος ισχίου. Σπάνια, αλλά επίσης σοβαρή επιπλοκή της ΕΜΚ, είναι η χονδρόλυση, η οποία χαρακτηρίζεται από σημαντική απώλεια αρθρικού χόνδρου του ισχίου. Άλλες επιπλοκές σχετίζονται με τα υλικά σταθεροποίησης, όπως είναι η κύρτωση, η χαλάρωση και η μετανάστευση του υλικού. Η προληπτική ήλωση του ασυμπτωματικού ετερόπλευρου ισχίου αποτελεί αντικείμενο επιστημονικής διαμάχης. Ανθεκτικό σε χρόνο και χώρο χαρακτηριστικό της ΕΜΚ αποτελεί η καθυστέρηση στη διάγνωση και - επομένως - στην αντιμετώπιση της. Η ύπαρξη υποκλινικής, αλλά εν δυνάμει επιδεινούμενης, ΕΜΚ, στοιχειοθετεί το αντικείμενο πολλών ερευνών. Δεν υπάρχει ομοφωνία σχετικά με την αφαίρεση ή μη των υλικών σταθεροποίησης, ιδιαίτερα εφόσον αυτά δεν προκαλούν συμπτώματα. Αυξανόμενο ενδιαφέρον παρουσιάζει ο ρόλος της αρθροσκοπικής οστεοχονδροπλαστικής για την πρόληψη και την πρόωμη αντιμετώπιση της μηροκοτυλίας πρόσκρουσης.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: επιφυσιολίσθηση μηριαίας κεφαλής, χειρουργικές τεχνικές, επιπλοκές

Isolated hamate dislocation with simultaneous carpometacarpal subluxation. A case report

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ABSTRACT

Background: Hamate dislocation is a rare injury resulting from high energy trauma of the hand. Isolated or combined with other injuries, volar or dorsally dislocated should be recognized and treated so as to restore anatomically adjacent carpal bony structures. Treatment can be closed or open with internal stabilization. Physiotherapy should follow until satisfactory joint motion and hand grip strength is achieved.

Case Report: We present an isolated volar hamate dislocation, with simultaneous ulnar translation of the fourth and fifth metacarpal bones, following a crush injury due to high pressure hydraulic machine. To the best of our knowledge, no such a case has been described. During open surgical exploration hamate was identified intact and was pinned to adjacent bones with Kirschner wires. Following intense physiotherapy the patient returned to previous level of working activity.

Conclusion: Open reduction and stabilization with K-wires can be an effective and definite surgical treatment in complex dislocations of the hamate.

KEY WORDS: hamate; dislocation; crush injury; carpometacarpal dislocation

Introduction

Isolated hamate dislocation was first described by Buchanan in 1882 [1]. As considered a rare medical case, combination with associated carpal or metacarpal traumatic injuries makes it even rarer. Usually it results from a high energy injury. We currently present a volar dislocation of the hamate, associated with carpometacarpal subluxation of the 4th and 5th metacarpal.

Case presentation

A 50 years old carpenter presented to the emergency department, following an open crush injury of his left hand and carpus that he sustained four hours prior to his arrival, caused by high pressure hydraulic machine similar to a punch press. He did not report any other injuries and was otherwise healthy. Full thickness, open lacerations were noticed at the thenar and hypothenar regions, as well

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Fig. 1 Anteroposterior X ray of the left hand. Diastasis at the base of the 3rd and 4th metacarpal and absence of the hamate is noticed

as at the dorsal side of his thumb and wrist. Edema and numbness were detected on clinical examination. The patient was not able to move his joints peripheral to the carpal joint, due to imperative pain, while there was slow-running blood flow in all digital vessels as confirmed by Doppler examination performed. Plain anteroposterior and lateral x rays revealed a complete volar dislocation of the hamate and ulnar dislocation of the ring and small finger (**Fig.1**). Computed tomography (CT) scan was unavailable at that time due to technical issues, so the patient was directly transferred to the operating room for surgical management.

Under general anesthesia a dorsal approach through the 3rd and 4th extensor compartment was performed, the retinaculum was dissected in a rectangular shape, with its base on the radial side, and extended the open wounds regions. The hamate was identified. No fracture of the hook was noticed. After the anatomical reduction of the hamate, carpal

instability was detected, due to the subluxation of the 1st, 3rd, 4th, and 5th carpometacarpal joints. Reduction and stabilization was achieved through k-wires fixation. The hamate was pinned directly to the capitate, the capitate to the scaphoid and the 1st row (**Fig. 2 a,b**). Gilula's arc was restored anatomically. No neurovascular injury was detected. Complete rupture of the extensor indicis and the extensor digitorum communis was restored anatomically. Wounds were closed as per standard approach and a palmar plaster cast was applied in neutral position for maintaining the restoration and for soft tissue healing.

The patient received intravenously dispersed antibiotics for 4 days switched to oral delivery, for 10 more days right after his discharge from the hospital as per standard protocol. No complications were documented postoperatively. K-wires were retracted 6 weeks postoperatively and a night splint was utilized for additional 6 weeks (**Fig. 3**) following intense physiotherapy. At the 1 year follow up, range of motion in all joints was almost painless and satisfactory as well as the grip strength. At that time, minimal radiographic changes of arthritis affecting the 4th and 5th carpometacarpal joint were noticed. The patient did not return for further follow up.

Discussion

Dislocation of the hamate was first described from Buchanan in 1882. [1] It is a rare injury and is usually associated with severe trauma, predominantly among manual workers. [2, 3] Volar dislocation is slightly more often than dorsal. It can be an open or closed injury [4], isolated [5] or combined with metacarpal or other carpal bone dislocation ⁶⁾ or even fracture. Our patient sustained a crush injury, followed by an isolated dislocation of an intact hamate bone. Simultaneous fracture of the hook of the hamate is unusual. Garcia-Elias described a classification for carpus dislocations, according to which the hand was divided in two columns, the radial and the ulnar one.⁷⁾ Injuries were classified as axial-radial, axial ulnar and axial-radial ulnar.

Possible mechanism of injury is still controversial. Pisohamate, capitohamate and intracarpal lig-



Fig. 2a,b Anteroposterior and lateral view immediately postoperatively



Fig. 3 Anteroposterior radiograph at 3 months follow up visit

aments provide rigid stability. Forces can be transmitted directly or indirectly. Volar dislocation with ulnar translation of the metacarpals probably occurs when the hand while being in flexion with ulnar deviation, the force is transmitted axially.⁵⁾ On the other hand fracture of the hook of the hamate occurs in plantar fascia's injury, though in our case not presented as expected.


A gap between the capitate and the pisiform is diagnostic in the hamate dislocation in the anteroposterior radiograph of the hand, while on the lateral film volar or dorsal translation can be easily noted. When fracture of the hamate is suspected, oblique and carpal tunnel views are diagnostic.⁸⁾ Albeit CT is more accurate, it should be performed only if the condition of the patient permits to do so. Additionally, it is rather helpful in revealing stress fractures, fractures of the hamate hook or small osteochondral lesions.

Reduction might be closed or open.⁹⁾ Closed manip-

ulation under general or local anesthesia, followed by casting for 6 weeks, is a successful choice in some cases.^{5,10)} In our case surgical management was indicated, due to the extensive laceration of the palmar hand. When closed reduction fails, or in cases of open frac-

ture-dislocations, open reduction and internal fixation is the treatment of choice. The use of K-wires in stabilization, for a period of 6 weeks, is simple and accurate. Our patient is one of the few ever managed with open reduction and K-wires fixation. Excision of the hamate has been also reported, especially when the ulnar nerve is under intense pressure by the dislocated carpal bones, with good clinical results.⁹⁾ Intense physiotherapy should always follow until range of motion and grip strength get restored.⁹⁾

Conclusion

Isolated complete dislocation of the hamate is a rare injury, while its simultaneous occurrence with subluxation of the carpometacarpal joints, is even less common. Open reduction through a dorsal approach and stabilization with K-wires is an effective surgical treatment method, with good postoperative results. 

Conflict of interest:

The authors declared no conflicts of interest.

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ΠΕΡΙΛΗΨΗ

Το τραυματικό εξάρθρωμα του αγκιστρωτού οστού του καρπού αποτελεί σπάνιο τραυματισμό. Πρέπει να αναγνωρίζεται άμεσα για την έγκαιρη χειρουργική αποκατάσταση είτε ως μεμονωμένη βλάβη είτε σε συνδυασμό με άλλες συνδεσμικές βλάβες του καρπού. Η αντιμετώπιση του τραυματικού εξάρθρωματος του αγκιστρωτού πραγματοποιείται με ανοικτή ή κλειστή διαδερμική οστεοσύνθεση. Παρουσιάζεται περίπτωση τραυματικού παλαμιαίου εξάρθρωματος του αγκιστρωτού οστού του καρπού με συνοδό ωλένια μετατόπιση του τέταρτου και πέμπτου μετακαρπίου ως αποτέλεσμα καρπο-μετακάρπιου εξάρθρωματος.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: αγκιστρωτό οστό, εξάρθρωμα, καρπομετακάρπιο εξάρθρωμα