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Pathogenetic and Clinical aspects

Melinda Witbreuk

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Aan mijn ouders

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CHAPTER 1

General introduction

Slipped capital femoral epiphysis (SCFE) is the most common non-traumatic hip disorder in adolescents, although its occurrence is rare. Sometimes it can be misdiagnosed as a traumatic femoral head fracture.
In SCFE, the physis is not strong enough to withstand the shear forces acting on the femoral head. This results in a displacement of the epiphysis relative to the metaphysis. The metaphysis shifts in an anterolateral and cranial direction and rotates externally. The epiphysis hereby remains in the acetabulum.
This disorder can lead to a restriction in movement and pain in the short term, and early symptomatic hip joint arthritis in the long term. It is also one of the few adolescent disorders that always needs surgical treatment to prevent an increase in slip of the femoral head, which can worsen the functional outcome. If left untreated, a deformity of the femoral head may gradually develop.

SCFE can compromise blood supply to the femoral head. The medial circumflex artery runs posteriorly of the femoral neck. A posteromedial displaced slipped femoral head may damage this artery which supplies the vascularity of the metaphysis and epiphysis. If the blood supply is impaired, avascular necrosis of the femoral head and neck can occur, leading to further deformity of the femoral head.

This thesis addresses different aspects of SCFE. The first question asked was whether the incidence of SCFE is increasing in the Netherlands? In the literature, results from other western countries (USA and Sweden) suggest an incidence of 10 to 80 cases per 100,000 population, compared to a much lower (but currently increasing) incidence of 1 to 2 per 100,000 in Singapore and Japan. In the Netherlands, all patients who are admitted to hospital are registered in the National hospitalization registration system (LMR). Two international classifications of disease codes, traumatic and the non-traumatic SCFE, were analyzed.

The second question of this thesis concerns the potential causes of a slip of the physes of the femoral head. The literature attributes slips to both biochemical and biomechanical causes. The slip occurs mostly in puberty, when the hormonal balance is changing in the body. Hypothetically, such hormonal imbalance could be the underlying cause of the slip. Although there is some histological research of the physis in SCFE, we are not aware of any published research about hormonal receptors in the physes in SCFE. To understand more about the hormonal imbalance, we reviewed the literature about which hormones could be involved

in SCFE during adolescence. Using this review, we conducted a histopathological study of the physes of SCFE patients and compared them to normal physes (which became available after amputation or epiphysiodesis for leg length difference).

Since the choice of surgical treatment remains controversial, especially in acute, unstable SCFE, we investigated how Dutch and British pediatric orthopaedic surgeons would treat this disease. All surgeons, members of the Dutch pediatric orthopaedic society (WKO) and the British society of children orthopaedic surgery (BSCOS), were asked to complete a questionnaire to quantify agreement and disagreement about treatment of acute, unstable SCFE between these two European countries. The Pediatric Orthopaedic Society of North America (POSNA) recently published a questionnaire on the same topic, and we compared it to our questionnaire results.

Currently, many articles focus on femoro-acetabular impingement (FAI) as a cause of early arthrosis. The metaphysis in SCFE can create an anterolateral prominence on the transition between femoral head and – neck and behaves as a CAM-type deformity lesion. With flexion of the hip, this can cause impingement on the anterior acetabular rim. Many operative techniques for FAI have been described, some with a large risk of complications. We looked into a patient population of SCFE to assess the results of an one-stage operation: a screw fixation of the SCFE simultaneously with a downgrading of the slip by an early Imhauser osteotomy. The Imhauser technique flexes, derotates and valgisates the proximal part of the femur. The metaphysis is shifted away from the anterior acetabular rim thus minimising damage of the anterior rim. Given that the osteotomy level is intertrochanteric, there is a minor risk of complications such as avascular necrosis of the femoral head. The subcapital osteotomies however, which are alternatives for treating FAI, report a high risk of avascular necrosis of the femoral head.

Because SCFE is uncommon, most healthcare providers will rarely encounter it. Consequently, a child with SCFE might be wrongly diagnosed or interpreted as being a femoral head fracture, especially in the acute or acute on chronic cases. There might even be a history of a traumatic fall with or without antecedent complaints. If the disorder is misinterpreted as a fracture, one might consider removing the screw before the end of skeletal growth. This, however, carries a severe risk of postoperative slip progression. In the last chapter we describe two patients who underwent such

a procedure, with the slip worsening after premature removal of the screw. Both patients needed a subsequent operation. This emphasizes the need to leave the screw in position at least until the end of skeletal growth. Misapprehension of this disease can lead to devastating results.

Aims of this thesis:

1 To review current literature regarding SCFE, published between 2008 and 2014. Based on this literature review, the current concepts regarding SCFE are presented.
2 To assess the incidence in the past decade (1998-2010) of traumatic and non traumatic SCFE in the Netherlands based on data from the national hospitalization system of the Netherlands and to focus on the sex ratio of SCFE.
3. To assess the literature regarding the hormonal balance changes in puberty related to SCFE and their effects on the physes. We focused on the role of hormones in possibly changing the physes in SCFE and potentially weakening the physes rendering them more vulnerable to forces acting upon them.
4. To examine the histology and histopathology of the physes with SCFE and compare this to healthy physes focusing on possible differences in hormonal receptors expression, an apoptosis marker and differences in vascularity.
5. To investigate how pediatric orthopaedic surgeons, members of the WKO Netherlands and BSCOS United Kingdom prefer to diagnose and to treat acute, unstable SCFE in order to quantify differences and similarities between them and compare them with the POSNA members in the USA.
6. To report the follow-up of SCFE patients who had an one-stage procedure with screw fixation and a downgrading of the slip by an Imhauser femur osteotomy. The aim was to prevent early impingement by changing the angle of the head relative to the acetabulum. The outcome parameters were clinical and radiological examination and the Harris Hip Score (HHS).
7. To report on two SCFE cases mistakenly diagnosed as Salter Harris fractures. In these cases, removal of the fixating screw resulted in a devastating deformity of the femoral head and a subsequent procedure.

CHAPTER 2.

Current concepts in Slipped Capital Femoral Epiphysis

A review of the literature 2008-2014.

Witbreuk MM, van der Sluijs JA, Jansma EP, van Kemenade FJ, van Royen BJ

Introduction.

Slipped Capital Femoral Epiphysis (SCFE) is an adolescent disorder of the hip in which the neck of the femur is displaced through the hypertrophic zone of the physis. The proximal femoral neck and shaft translate and rotate anteriorly, superiorly and externally relative to the femoral head, leaving the femoral head in the acetabulum stabilized by the ligamentum teres. The displacement of the femur neck may cause pain and limping at a young age and can cause osteoarthritis at a later stage, possibly initiated by changes in biomechanics and femoro-acetabular impingement (FAI).

The cause of SCFE is probably multifactorial: biomechanical and biochemical factors have been implicated. SCFE is often diagnosed late because most healthcare providers are unfamiliar with this condition. The slip can become progressively severe if not diagnosed early. Healthcare providers should be made more aware of the early signs and symptoms, so that appropriate imaging may lead to earlier recognition and treatment of this motion-limiting disease [104].

SCFE is the most common hip disorder in adolescence, but its incidence is still very low. New literature, however, describes an increase in SCFE incidence, probably due to a general increase in body mass index (BMI). Historically, obese boys were considered to have a higher risk of developing SCFE, but new literature shows girls are becoming increasingly susceptible to it. New insights into pathogenesis provided by modern histological techniques are showing that understanding the roles played by biomechanical and biochemical factors could be important in finding the cause of SCFE. Children in adolescence and with known endocrine disorders are more vulnerable to developing SCFE, reflecting the vulnerability of a weak physis to forces applied to the femoral head.

The treatment is controversial for some subgroups of the disorder. The basic treatment of SCFE to prevent immediate deterioration is to stabilise the slip using a percutaneous screw fixation in the femoral head, but the best method for improving the outcome of secondary deformation of the head is subject to debate.

Numerous papers have been published about SCFE. The discussions in the literature focus on the interaction of biomechanical and biochemical causes for SCFE, the changes in its diagnostics and its treatment. This review aims to provide a comprehensive guide of all recent research concerning SCFE. Aspects of SCFE covered by this review include: general aspects, epidemiology, etiology, pathogenesis, diagnosis, different methods of treatment, complications and prognosis.

Methods.

Literature search.

We performed a search in the PubMed database from January 2008 until January 2015. The following search terms were used and included controlled terms from MeSH as well as free text terms. The references of the identified articles were searched for in relevant publications.

"slipped capital femoral epiphyses" [MeSH Terms] OR ("slipped" [tiab] AND "capital" [tiab] AND "femoral" [tiab] AND epiphys* [tiab]) OR (slipped [tiab] AND upper [tiab] AND ("femur" [MeSH Terms] OR "femur" [tiab] OR "femoral" [tiab]) AND ("epiphyses" [MeSH Terms] OR epiphys* [tiab])) OR scfe [tiab] OR sufe [tiab] OR ("slipped" [ot] AND "capital" [ot] AND "femoral" [ot] AND epiphys* [ot]) OR (slipped [ot] AND upper [ot] AND ("femur" [MeSH Terms] OR "femur" [ot] OR "femoral" [ot]) AND ("epiphyses" [MeSH Terms] OR epiphys* [ot])) OR scfe [ot] OR sufe [ot] AND ("2008/01/01" [PDAT] : "2015/01/01" [PDAT])

Selection Phase.

Two independent researchers screened all titles of the abstracts to determine eligibility. If necessary, the full text of an article was also checked for the eligibility criteria. Differences in opinion were resolved by consensus procedure. Exclusion criteria were: articles not related to children or adolescents, publication types like case reports, conference abstracts and articles discussing complications in later life. Articles other than those written in English, Dutch or German were also excluded. Full texts of articles were obtained for further review.

Results.

The literature search generated a total of 434 references in PubMed, 47 additional studies identified through reference checking were included. 481 Papers were selected based on title and abstract. 314 Papers were excluded based on the above-mentioned criteria. 167 Papers were included in this review.

Epidemiology.

The average age at diagnosis of SCFE is 13.5 years for boys and 12.0 years for girls [68].

Previous reviews found an incidence of 0.2 to 10.08 per 100,000 population [69]. New data showed that the incidence of SCFE differs among countries. The numbers of incidence in the literature are difficult to compare because age group criteria and methods of estimation differ among studies. In the Western world (Europe and USA) the incidence seems to be higher than in Asian countries like Japan. This may be related to the difference in average child body weight among races [69]. Increased SCFE incidence were found in African American and Polynesian populations, with the Maori population having the highest incidence, 81:100,000 [101]. Recent studies show that globally, there is an increase in children with SCFE and obesity [15, 90, 92, 129]. Interestingly, the children who have bilateral disease seem to have a higher BMI [17]. The literature suggests a male predominance in SCFE cases. The sex ratio in children with SCFE, however, seems to have changed over time, from 90% male during the 20th Century to 60% recently [44]. In the Netherlands the change is more pronounced, with an equal number of boy to girl ratio in SCFE cases being recorded in the past decade [153].

Wabitsch et al. [145] examined 411 overweight and obese children. Of these patients, 54 had either hip or knee pain or limited motion of the hip (< 90° flexion and < 10° internal rotation). These 54 patients underwent anteroposterior (AP) and axial radiographs of the pelvis and femoral head. Of this clinically conspicuous group, 11 patients had signs of SCFE (based on an abnormal head-neck angle), i.e. 20% in this group and 2.7% of the total cohort. Lehmann et al. [63] examined a population based cohort of 2072 patients between 2007 and 2009, all born in 1989. His radiological findings were consistent with possible prior SCFE (based on the Lateral radiograph headshaft angle > 13°) in 6.6% of these asymptomatic young adults. Based on these two conclusions, we can assume that the incidence of SCFE might be even higher than suggested by the literature.

Etiology.

Previous reviews suggest that the cause of SCFE is probably multifactorial. Biomechanical and biochemical processes both influence the adolescent physis. Being overweight or obesity are considered a biomechanical factor, since at least 50% of the children with SCFE are above the 95th percentile for weight, based on age and length [69]. Other mechanical factors associated with SCFE are femoral retroversion and increased physeal obliquity [109]. In a finite element model, a varus hip load in combination with femoral retroversion in an overweight child can create physeal strains above the yield point, possibly resulting in a slip [31, 38]. The slope of the femoral growth plate on an AP radiograph shows the main increase in steepness between 9 and 12 years old which may be a factor contributing to SCFE within this time span [83].

Other studies have focused on the shape of the femoral physes and acetabula. The changing shape of the physis from a pleated towards a more spherical physis in puberty could be one of the risk factors for SCFE [53]. The epiphyseal tubercle on the inferior surface of the capital femoral epiphysis relatively decreases relative in height and surface area with increasing age. This may also explain the vulnerability of SCFE in adolescence [67].

In addition, changes in the acetabulum in SCFE are described. CT scans have shown increased retroversion of the upper quarter of the acetabulum in SCFE patients. Whether this is a primary or secondary response is unclear [86]. The acetabular version between the affected and unaffected side does not appear to differ [76]. Interestingly, the contralateral acetabulum in unilateral SCFE compared to age and sex-matched controls has significantly higher prevalence of acetabular retroversion [117]. Gehart et al. [36] could not confirm the acetabular retroversion in SCFE. In this study, the acetabular version of 14 cadaveric pelvis with post-SCFE deformity were compared to 200 normal cadaveric pelvis, all age, sex and race-matched, and there were no differences between affected and unaffected sides, in a same specimen as well as in specimen with or without SCFE. Poseszwa [107] describes patients with SCFE as appearing to have, based on a radiographic standardized supine AP view of the pelvis, a deep acetabulum where the medial edge of the acetabulum is medial of the ilioischial line. This could lead to physeal instability as SCFE develops. In the literature, the valgus type SCFE accounts for approximately 4% of all SCFE cases (most are varus type SCFE). Valgus SCFE patients were younger, had lower risk of bilateral disease and females were more susceptible to it. The severity of

patients with valgus SCFE seems to be less than those with varus SCFE. The disorder might be more difficult to diagnose since the Klein's line is normal (see radiological diagnosis). Only the lateral radiograph of the hip may reveal the slip. Valgus type SCFE may be associated with coxae valgae, hypopituitarism and stickler syndrome [57, 70, 125].

Bilateral disease in SCFE is reported in 18-50% of cases [69]. The risk of bilateral disease can be predicted by measuring the posterior sloping angle (PSA) on an axial radiological view of the contralateral physis [13, 58, 97, 102, 162]. Alternatively, as means of predicting the risk of bilateral disease, could the modified oxford bone age score be used in unilateral SCFE. This bone age score incorporates 3 consecutive stages of maturation for 5 features: the femoral epiphysis, the greater trochanter, the lesser trochanter, the triradiate cartilage and the ilium. The risk of a contralateral slip was an 89 % probability, if a wide open triradiate cartilage was present (score of 1). In these cases it was concluded that a prophylactic contralateral pinning of the femoral head was advisable [108]. Interestingly, children with obesity can lower the risk of bilateral disease when reducing weight after unilateral SCFE [91].

Biochemical processes and endocrine factors are associated with SCFE. The timing of this disease is around puberty, a time of hormonal imbalance and rapid growth. An increased incidence of SCFE has been found in children with hypothyroidism, hypogonadal states, vitamin D deficiency and renal osteodystrophy [69].

A definitive hereditary pattern in SCFE has never been established. Rennie et al. [112] proposed an autosomal dominant inheritance pattern with incomplete penetrance in SCFE. The risk of developing SCFE by a second family member was 7.1%. Tins et al. [138] claim that an abnormal cartilage formation might be related to SCFE. They found an increased thickness of both the cartilage of symphysis width and the unaffected hip joint width in SCFE compared with the normal widths. They concluded that either an increased cartilage formation or a decreased maturation could explain the vulnerability in SCFE.

In conclusion, SCFE is most likely the result of a multifactorial event during adolescence when height and weight increase dramatically and the delicate balance between the various hormonal equilibria can be disturbed. There are no biochemical screening or diagnostic tests available yet to predict patients at risk [151].

Pathogenesis.

Histological studies of tissue obtained from biopsies during surgery for SCFE show some characteristic features of the physis of the femoral head. Changes in longitudinal orientation of the cartilage cells of the physis, which are normally parallel to the axis of the bone, are seen in tissues taken from biopsies in SCFE. In SCFE, pathologic tangential forces can damage the hypertrophic cartilage. Because of the longitudinal orientation of these fibers, this zone is least protected from these shearing forces [25]. Obviously as biopsies were taken after the slip occurred, it is not clear whether the observed changes in cell orientation are present before or after the slip occurred.

The resting zones of the physis appeared to be relatively normal in SCFE [3, 40, 49, 80]. The proliferative and hypertrophic zones of the physis in SCFE were wider than in normal physes and showed irregular columnar organization with gradual loss of longitudinal septa and a diminished number of chondrocytes in each column [3, 4, 40, 49, 80]. Interestingly, Adamczyk et al. [2] showed that apoptosis was increased throughout the physis in SCFE, in contrast with controls where apoptosis was limited to the hypertrophic zone. The chondrocytes showed intracellular abnormalities [4, 30, 49]. An increase in nuclear and cytoplasmic density was seen in the proliferative and hypertrophic chondrocytes with SCFE and there was an increase in cytoplasmic glycogen [4, 30]. Other authors, however, could not confirm these findings [3, 80]. The extra cellular matrix (ECM) of the physis had abnormal longitudinal septa with a collagen deficiency [4, 30, 49]. The amount of proteoglycans in the ECM was moderately less in the matrix of the physis in SCFE compared to normal [3, 4, 30]. Also, abnormal proteoglycans were found in the ECM [49]. Matrix vesicles, secreted by hypertrophic chondrocytes, were more abundant than in the controls [4, 30, 49]. Matrix vesicles contained calcium phosphates, hydroxyapatite and matrixmetalloproteinases (MMP). The contents of these vesicles change the structure of the ECM and begin the process of calcification of the matrix [35]. Lacunar spaces in the hypertrophic zones were seen with reactive changes showing callus formation [3, 40, 80].

Scharschmidt et al. performed laser capture microdissection followed by a quantitative reverse transcription-polymerase chain reaction analysis of mRNA on physis tissue of SCFE obtained by biopsies. They observed downregulation of both type 2 collagen and aggrecan in the physis of patients with SCFE [122]. Of interest is a study of Tank et al. [135] where they administered 6-propyl-2-thiouracil (a drug given for hyperthyroidism to decrease the amount of thyroxine) to 11 week old

miniature swine. They harvested the hind limb proximal femoral physis at 25 weeks. Compared to the two controls the two hypothyroid swine showed disorganization and widening of the physis and loss of chondrocyte columns and cells. Also the swine gene expression showed inhibition of type 2 and 10 collagen and aggrecan, similar to the human physis in SCFE.
In conclusion, the physis in SCFE shows histological differences compared to normal physes in columnar organisation, on a cellular level and in the extra cellular matrix. The fundamental problem is that the role of these described changes is unknown. It is unclear whether they are causal or adaptive. Some of these changes can also occur as endocrine or metabolic abnormalities.

Diagnosis.

Primary healthcare providers are often unfamiliar with SCFE and do not recognize this hip problem in adolescents, thereby delaying the diagnosis which results in severe consequences. A previous study described an average duration of 5 months before symptoms occur and SCFE can be diagnosed [69]. Of the patients with acute/unstable SCFE, 88% have antecedent symptoms more than a month in advance. Early diagnosis is critical to prevent a morbid, unstable SCFE [78]. Clinical examination often reveals a limp and localized pain in the groin, hip, thigh or knee. On physical examination, decreased internal rotation and flexion of the slipped hip joint is found. The sign of Drehmann, which features external rotation and abduction when flexing the hip, is related to the existence of femoral acetabular impingement [52].
Actual diagnosis of SCFE is confirmed by radiographic examination. Detection of the subtle signs of early SCFE from an anteroposterior (AP) radiograph of the pelvis requires a trained eye. The `metaphyseal blanch sign` is an overprojection on the anteroposterior radiograph of the femoral head epiphysis slipping posteriorly of the metaphysis. The Klein's line is a line drawn over the superior part of the neck and is supposed to intersect the epiphysis of the head on the AP radiograph. In SCFE, however, this Klein's line does not intersect the epiphysis, or show a difference in the maximal width between the epiphysis compared to the opposite site in unilateral disease. [39, 50, 106]. Its sensitivity is mainly limited in the valgus, and in mild and moderate slips [106].
Another diagnostic can be found on an AP radiograph of the pelvis; part of the inferior metaphysis is normally projected over the posterior cortex of the acetabulum, which has disappeared in SCFE. A new pathognomic finding has been

described by Song et al. [130]: On the AP radiograph of the pelvis, a decrease in acetabulo-trochanteric distance is found on the affected side compared to the normal side in 76 % of all cases.
The frog lateral radiograph of the femoral head makes it easier to diagnose SCFE. The Southwick classification can be made on the frog lateral (See radiological classification) [18]. In fact there is not a pure AP or lateral deformity, but an oblique plane deformity in SCFE. To evaluate this deformity accurately one can measure the degree of slip on an AP radiograph, and the axial deformity on a CT or MRI scan and calculate the real oblique plane from these angles [24].
In preslip or an early slip, the radiograph can be normal. Bonescintigraphy and MRI can be used for diagnosis in early SCFE. On the MRI one can detect a widening of the physis with bone oedema on the metaphysis, joint effusion and synovitis [50, 139]. Also, in an acute slip, the bonescintigraphy and the MRI can detect early avascular necrosis by impairment of the vascular supply to the femoral head due to the position of the metaphysis relative to the head or alternatively, due to the instability of the head [50, 113, 139].
In a later stage of SCFE femoro-acetabular impingement can occur (see FAI). Impingement by prominence at the femoral head-neck junction on the anterior acetabular rim may cause early osteoarthritis. Nőtzli et al. [93] developed a method to measure the asphericity of the femoral head and the cam-type deformity by the alpha angle: an angle between a line from the centre of the femoral head through the middle of the femoral neck and a line through a point where the contour of the femoral head-neck junction exceeds the radius of the femoral head .
In conclusion, SCFE is difficult to diagnose due to unfamiliarity with the diagnosis by healthcare providers and due to a challenging presentation of complaints. Traditionally the diagnosis is made on a radiograph of the pelvis. The AP view might be subtle to see a mild slip, a lateral radiograph of the proximal femur makes it easier. Different ways of investigating SCFE with radiographs, CT and MRI are discussed. Bonescintigraphy can be useful in diagnosis AVN pre and post operatively.

Classification.

Several classification methods exist based on clinical radiological features.
SCFE can be classified based on history according to the time of complaints of the patient in: preslip, acute, acute on chronic or chronic [10, 69]. The preslip occurs prior to the actual slipping through the physis. The patient provides a history of an episodic limp and limb weakness associated with pain in the groin, anterior

thigh or knee. The radiographs show no physeal slippage but might reveal a minor widening and fuzziness of the physis. Patients with symptoms less than 3 weeks old are defined as having acute SCFE. On the AP and lateral radiograph of the proximal femur, there is an abrupt slip of the physis visible. Patients with more than 3 week old symptoms are defined as having chronic SCFE. This accounts for 85% of all slips. The radiographs can show a variable amount of remodelling of the femoral neck. Patients with acute on chronic SCFE have pre-existent pain but the pain has aggravated acutely within the last 3 weeks.

The Loder classification is based on either the ability to walk with or without crutches on the affected hip (stable) or not (unstable). This classification is a prognostic classification, the unstable group having a higher incidence of avascular osteonecrosis of 47% [71].

Ziebarth et al. [164] evaluated the clinical classifications for acute and acute on chronic as well as an unstable hip intraoperatively, by identifying an intact or disrupted stability of the femoral head in situ. Interestingly, these clinical observations inaccurately identified the intraoperative mechanical stability.

The radiological (Southwick-angle) classification describes the amount of slip on a frog lateral radiograph of the proximal femur of the hip. The Southwick angle is the line perpendicular to the connecting two points at the posterior and anterior tips of the epiphysis at the physis. A third line is drawn down the axis of femur. Angles are classified as severe, modest and mild at > 50 degree, 30 to 50 degrees and below 30 degrees respectively [133].

In conclusion there are three ways of classification of SCFE, based on history, clinic and radiograph. The clinical and radiographical classifications can be used for prognosis of SCFE.

Treatment.

The ideal treatment for SCFE is defined as the treatment that has the best outcome for the hip joint, while taking into consideration the complications that can occur with the different treatments options, aiming for a good long-term follow-up result. Management of SCFE is controversial and only level 4 and 5 evidence exists [156]. Treatment options appear more subject to a surgeons' preferences and experiences than to evidence of superiority of a particular treatment. Avoiding the potential complications like progression of the slip, chondrolysis and avascular necrosis is probably the most important initial goal in the treatment of SCFE [69].

Primary Treatment.

Conservative Treatment.

Although conservative treatment with a plaster cast has been described [105], most surgeons would choose for an operative treatment. Santini described 18 patients with 26 SCFE hips who were referred to him with non-surgical treatment. Retrospectively, 73 % of these hips showed progression of the slip over time, concluding that a conservative treatment is an poor option for this severe disorder [121].

Single screw fixation

The favoured surgical procedure is one percutaneous single screw fixation with intraoperative fluoroscopy in SCFE [9, 73, 88, 131, 134, 142]. The literature highlights this as the preferred method for stable and unstable mild slips [1]. Single screw fixation was compared to bonepeg epiphysiodesis, based on 38 year follow up, with the screw fixation being chosen as the best option, given that this technique is less demanding and because postoperatively no traction is needed [147]. There appears to be no consensus regarding the best treatments of moderate and severe slips. In the latter slips remodelling potential of the deformity of the slipped femoral head may be insufficient to create a congruent joint and leaves a joint with reduced mobility and may cause femoral acetabular impingement, which will be discussed later.

Unstable SCFE treatment.

There seems to be no consensus between countries or continents about how to treat unstable/acute SCFE. There are different approaches in diagnosis and treatment between the UK and the Netherlands which also differ from those of the Pediatric Orthopaedic Surgeons North America (POSNA) [87, 150]. Overall, the UK and the Netherlands diagnosed patients similarly and agreed with the need for urgent management. Sixty-six per cent did not reposition the slip. Significant differences were observed in attitude towards single screw usage, prophylactic pinning and screw removal both between the two European countries and compared to North America. The discussion to reduce the slip and the timing of this reduction, if done, is ongoing in the literature. The principal risk in this treatment is avascular necrosis of the femoral head. Sonnega et al. [131] used an EPOS questionnaire study and found that the majority of surgeons use reduction by only gentle positioning of the hip in the fracture table and a percutaneous screw fixation.

Generally, the recommendation for treatment of unstable slips is gentle reduction, decompression and internal fixation within 24 hours of aggravation of the complaint [73, 74].
Despite this, no statistical differences was found in a meta-analysis study by Lowndes et al. [74]. They found 4 studies regarding reducing or not reducing unstable slips and 5 studies regarding a time window of 24 hours. Their advice was that reduction should be undertaken with great caution and probably within 24 hours. Bonescintigraphy is a sensitive predictor for development of AVN in unstable SCFE. This can be used preoperatively to diagnose AVN, before any treatment has been carried out, which will worsen the prognosis of the slip [113].

Screw position and amount of screws.

For a more accurate position and length of the percutaneous cannulated screw, biplanar fluoroscopy [148] or the use of an intraoperative arthrogram [157] has been advised. Senthi [124] recommends a CT scan if there is any doubt about the position of the screw. Intraoperative radiographs overestimate the distance between screw tip and the subchondral bone of the femoral head. A suggestion is to keep the screw tip at least 6 mm away from the subchondral bone of the femoral head during fluoroscopy on the AP plane and 4 mm away from the subchondral bone of the femoral head in the lateral plane intra-operatively. Fully and partially threaded screws for fixation were tested for stability. No biomechanical benefit was found between fully and partially threaded screws in this in vitro model with porcine femurs. However they mentioned that it may differ after bone healing, with fully threaded screws eventually providing greater stability [84]. Whether to use one or two screws is debatable. In a porcine model, one and two screws were tested in a displaced and nondisplaced model. The conclusion was that the in situ fixation with one screw is sufficient in a nondisplaced SCFE, while two screws might optimize a displaced slip [123]. Currently, the recommended entree-point for the percutaneous cannulated screw is anterior to cross the physis perpendicularly and to position the screw point in the middle of the femoral head. Merz et al. [79] compared anterior and lateral entree-points for the percutaneous screw in 22 paired porcine femurs and found no statistically significant difference in load to failure and stiffness of their model. However, Hagiwara et al. [41] showed a 53% slip progression after a percutaneous screw fixation. Multiple regression analysis showed that a lateral entree-point for a cannulated screw insertion prevented postoperative slip progression.

Prophylactic pinning of the contralateral hip.

Bilateral SCFE involvement is reported between 15 and 50% in the literature [11, 69]. Controversy exists over prophylactic pinning. Prophylactic pinning can be safer and more preferable to observation alone to prevent AVN and slip severity on the contralateral side [11, 154, 159]. Alternatively, one must consider the possible complications caused by prophylactic pinning like chondrolysis, AVN and peri-implant fracture [59, 119]. Generally, most articles suggest observation seems to be the most appropriate treatment on the contralateral site. Observation might not be appropriate in a very young child, a child with a known metabolic or endocrine disorder or in a child with a severe unstable unilateral slip. In these situations contralateral screw fixation might be warranted [43, 47, 55]. Wensaas et al. [147] reports good long-term results after untreated contralateral hip in unilateral SCFE. Within their group, only 5 of 40 patients with a mean FU of 36 years were present with a poor (missed SCFE?) outcome on the contralateral side, although the Nötzli's alpha angle was higher in the contralateral hip group compared to normal hips. Vlachopoulos et al. [144] reported persisting growth after prophylactic single cannulated screw fixation (10 out of 11 patients), necessitating a thorough follow up of the prophylactic pinning on the contralateral side. Some authors recommend a prophylactic percutaneous screw fixation on the contralateral side if the posterior sloping angle (PSA) is 12-19 degrees or higher (see etiology) [58, 98, 102, 162].

Removal of screw implants in SCFE.

There is no evidence promoting routine removal of implants in children, especially in SCFE where the complication rate of removal is high (34%) [111]. Removal of screw implants before closure of the physes can cause a further slip in the physes [29]. Despite these known complications, in the survey of the Netherlands and the UK, 21% (33 versus 17%) respondents admitted to remove the screw implants whilst the POSNA reported that in 12% [150].

Secondary reconstructive treatment.

Different osteotomies have been described in the literature for stable SCFE, before or after the physes are closed. Sonnega et al. [131] performed a survey among the members of the European Pediatric Orthopaedic Society (EPOS) and state that the spread of more complex techniques is slow among the participants of the survey. Numerous osteotomy techniques have been described: before or after the physis is closed, one stage osteotomy with screw fixation, and osteotomies on

different anatomical levels of the proximal femur in stable and unstable slips. Most osteotomies described in literature are discussed here.

Corrective osteotomy through the physis.

A corrective osteotomy through the physis such as the Dunn or Fish osteotomy is perfect for the reconstruction of the anatomy, but has a high risk of complications occurring like avascular necrosis and fixation failure [61, 69, 143]. Alshryda et al. [6] compared retrospectively a group of moderate and severe SCFE cases, one group treated by in situ screw fixation with no reduction and another with Fish osteotomy. They claim that both the groups showed equal numbers of patients suffering from AVN (around 30%), and they concluded that using a Fish osteotomy was preferable for the better anatomical position and the AVN was caused by the vascular damage and not by the osteotomy.

Ganz (2011) [34] introduced the technically more demanding method of surgical dislocation and open reduction of the slipped epiphysis (modified Dunn). This technique has until now only a few users. By extending the retinacular flap to preserve the vascular supply to the femoral head containing the primary perfusion and by dislocation of the femoral head for the osteoplasty, Ganz claims to see less complications of AVN of the femoral head. Even so, apart from it being technically demanding, it is possible that uncertainty about long-term prognosis and the increased AVN rate if performed by less experienced surgeons, are other factors limiting its use [7, 33, 48, 65, 75, 77, 120, 128, 131, 137, 163]. Novais found superior results with the modified Dunn procedure in comparison with the in situ percutaneous screw fixation for severe SCFE [94]. Anderson [8] performed a subcapital femoral osteotomy in the chronic slips after fusion of the growth plate and describes two out of 12 hips with AVN postoperatively. Ten out of 12 hip joints showed acetabular hyaline cartilage lesions which were caused by repetitive mechanical abrasion of the prominent metaphysis against the anterior rim of the acetabulum. The average time after pinning in situ for this procedure was 29 months. He furthermore states that this procedure carries out a significant risk of major complications. Souder et al. [132] advises only to perform the Ganz/modified Dunn in unstable slips. The rate of AVN is similar in this osteotomy compared to the in situ epiphysiodesis. In stable slips, a higher risk of AVN is found (20% Ganz versus 0% in situ pinning).

Concluding: results of performing a corrective subcapital osteotomy appears to be dependent on the experience of the surgeon. If a subcapital osteotomy is performed the risk of AVN should be taken into account.

Intertrochanteric osteotomies.

The intertrochantic osteotomies do not correct the deformity completely, but can safely realign and downgrade the severity of the slip, especially if this procedure is carried out at an early stage [28, 32, 115, 152]. This so called Southwick or Imhauser osteotomy can be combined with an additional open femoral osteoplasty of the cam lesion with a dental burr decreasing of femoral acetabular impingement in time [12].

Lino et al. [66] describes a downgrading of the slip after the Southwick osteotomy from 56.9 degrees to a 19.1 degrees Southwick angle on the lateral radiograph. After an intertrochanteric flexion rotation osteotomy the clinical examination values and gait kinematics improved significantly. The short-term impact on the quality of life was shown in the improvements of the patient related outcome measurement (PROM) for children: the pediatric outcomes data collection instrument (PODCI) scores on basic mobility, sports function and global function [20]. The fixation of a Southwick osteotomy can be performed either by angle blade plate fixation or by an external fixation [54].

It is important to know that on evaluating a standard AP and frog lateral radiograph, the headshaft angles might be over- and/or underestimated. The preoperative planning of an osteotomy might be safer in future with a 3-dimensional CT [85, 114].

Arthroscopy in SCFE

A fairly new technique is the arthroscopic management of the femoroacetabular impingement by femoral neck osteochondroplasty. It maybe questioned if chondrolabral pathology is prevented by the femoral neck osteochondroplasty. Wylie et al. [158] found in all 9 arthroscopically treated patients, after an in situ screw fixation, some degree of labral and acetabular cartilage injury. After the osteochondroplasty, the alpha angle, and the functional outcomes are improved significantly. So far this treatment modality is forthcoming and it is yet unknown if it will prevent arthrosis at the hip joint [136, 160].

Complications associated with SCFE.

Avascular Necrosis.

A meta-analysis estimated that between 1993 and 2009 AVN occurred in 5.3 % of cases after surgical procedure in SCFE, but chondrolysis was rare with an estimated risk of 0.8 %. The risk of AVN in unstable SCFE was 9.4-fold greater [141].

Other authors recite 20% of development of AVN in all acute, unstable SCFE [69, 96, 110, 161]. Currently, it is not yet known which treatment can lower this rate. Immediate reduction, capsulotomy and decrease of the intracapsular pressure or an open reduction and fixation modified Dunn procedure have all been described for reducing the rate of AVN. [23, 72, 75]. AVN in acute SCFE seems to develop significantly more often in younger patients, with a shorter duration of prodromal symptoms [118].

In unstable hips, an incidental/gentle reposition is only recommended within 24 hours after the acute slip. After this time-span the incidence of AVN is likely to rise [100, 103, 142]. The slip severity before gentle manipulation does not seem influential [118]. Parsch et al. [99] claim less AVN (4.7%) in unstable SCFE after capsulotomy, evacuation of intra-articular hematoma, controlled gentle reduction and fixation of the reduced physis by smooth K-wires. Herrera-Soto et al. [46] describes an increased intra-capsular pressure (48mmHg) in unstable hips, which is about double the pressure of the unaffected side (23mmHg). Also, gentle reduction significantly further increased the pressure (75mmHg). They claim there is a need for urgent capsulotomy in unstable SCFE, especially around the gentle reduction of this slip. Possibilities after AVN are limited. Vascularised fibular grafts after AVN in SCFE seem to improve the Harris hip score (HHS) postoperatively, but five out of 52 patients received a THP after 8 years [16]. Articulated hip distraction did not improve pain in SCFE. Definitive surgical procedures, such as total hip prosthesis or arthrodesis are not postponed after distraction, meaning that distraction does not change the outcome of the patients with SCFE [37]. Bisphosphonate therapy, to preserve femoral head sphericity and congruence, is safe to give to children but whether or not it can prevent complications due to AVN in SCFE needs further study [51].

In conclusion: avascular necrosis of the femoral head is a devastating complication of SCFE. In unstable SCFE the risk is considerably increased. Accidental reduction of the slip within 24 hours and capsulectomy after the percutaneous pinning is advised. It remains unclear whether other surgical procedures as modified Dunn or open reduction will improve the outcome.

Prognosis.

The Southwick classification is important for the long-term prognosis of SCFE. Patients with mild SCFE (<30 degrees) have good prognoses, but patients with moderate and severe SCFE have an increased risk of developing osteoarthritis later

in life [19, 95]. In the long-term, osteoarthritis can be triggered after repetitive early mechanical abrasion of the prominent metaphysis (cam-type lesion) against the anterior rim of the acetabular cartilage [64, 140]. Although most slips have some remodelling potential this may not be enough to prevent osteoarthritis [5, 14, 155]. Bone peg epiphysiodesis was compared in a long-term outcome study to single screw fixation. The outcome was good (HHS, no pain, no total hip replacement) in 69% of cases and there was no significant difference between these two techniques in chronic SCFE [147].

The functional outcome measured by mean Iowa hip score in 105 patients with one single screw fixation in stable SCFE grade 3 (more than 60 degrees slip) showed good or excellent results in 80 patients with a minimum follow-up from 5 years. Younger age, with more remodelling capacity, and adequate placement of the screw appeared related to a good outcome [21].

Larson et al. [60] reported that in their institution all grades of SCFE were treated by only single screw fixation. Reconstructive surgery, femoral osteotomy, surgical hip dislocation and total hiparthroplasty, was necessary in 21 (12 %) of 176 hips after a FU time of 16 years, but one third of the remaining patients complained commonly about persistent mild hip pain. There is a direct relationship between the degree of displacement in SCFE and the outcome and development of degenerative disease [19, 22, 42, 56, 147].

Functional impairments in SCFE patients can be found even after growth arrest. Westhoff [149] performed gait analysis on 37 patients with SCFE after growth arrest. The worst radiological subgroup revealed an increase in step width, sagittal range of motion of the pelvis and foot progression causing significant deviation in gait parameters. This could be due to the disease or be specific to the constitution of these patients (high BMI).

Femoro-acetabular impingement (FAI).

FAI after SCFE is caused by the abnormal morphology of the femur head after the slip, which can result in increased local contact forces between the metaphyseal bump of the femoral head and the anterior labrum of the acetabulum during hip motion. Prevalence of FAI, by a camtype deformity (bump formation on the edge of the femoral head and neck), was also found in asymptomatic volunteers and is reported in 14-24% of cases. [126].

In recent literature, the occurrence of FAI has been described in detail. It is caused by posteromedial displacement of the femoral head leaving an anterolateral

metaphyseal bump on the proximal femur. Usually, FAI is diagnosed on a radiograph. MRI can also be useful in measuring the aspherity of the head and the cam-type deformity by the alpha angle by Nötzli [81, 93]. Also on MRI, cartilage quality appears different in SCFE compared to the controls and, in addition, there is no relationship among clinical symptoms such as pain or hip function impairment [56, 82]. Delayed enhanced magnetic resonance imaging (dGEMRIC) in the mid-term follow-up of SCFE is also sufficiently sensitive to reveal degenerative changes, even in the absence of joint space narrowing that seems to be related to the degree of offset pathology [167].

Intraoperative cartilage damage of the acetabulum in SCFE produced by anterior cam impingement has been observed in 89-100% of cases, even in mild SCFE [62, 127, 165]. In a long-term study, Murgier et al. [89] found a direct relationship with the severity of slip and the existence of FAI. However, in a gait analysis study there was no relationship between the degree of radiographic deformity (Southwick angle, Klein's line and Nötzi angle) and the severity of kinematic deviations [116]. Castaneda et al. [22] describes an 80% occurrence of FAI after 20 years of follow ups on 122 patients with stable SCFE hips treated with in situ fixation. Although not every radiological FAI will progress to osteoarthritis [45], the questions are which ones will progress, which hip will become symptomatic and which hip may need treatment? There seems to be no linear correlation between offset pathology and joint degeneration in patients with SCFE after intermediate FU (11.1 ± 3.8 years) [166]. The alpha angle correlates most strongly with FAI. Of 49 hips in 36 patients with SCFE (follow up mean 6.1 years) 32% had clinical signs of impingement at skeletal maturity. No correlation with the Southwick angle or Loder´s classification was found [27]. Wall et al. [146] confirmed this, finding no correlation between the Southwick angle and long-term hip function in 32 patients with 38 affected hips. In addition to the above some concluded that timely remodelling after screw fixation of SCFE showed significant improvement of the femoral head neck relationship [5, 26].

In conclusion, FAI is caused by the metapyseal prominence (cam-type lesion) on the femoral head and is most likely the cause of osteoarthritis in later life. The abrasion on the anterior part of the acetabulum caused by the cam-type lesion is observed intraoperatively and on MRI. The question arises whether FAI is correlated with a worse clinical outcome on the long-term.

Conclusions.

Slipped capital femoral epiphysis (SCFE) is the most common adolescent hip disorder. Historically, the disorder was more common in boys, but recently sex ratios have become more even. In the Asian and Western literature an increase in incidence of SCFE has been found. Rising incidence is most likely due to increased BMI amongst children. The debate whether the disorder is more biomechanical, or biochemical or a combination of both is ongoing. The standard treatment for stable SCFE is single screw fixation. There is extensive discussion in the current literature regarding the treatment of unstable slip, treatment with different kinds of corrective osteotomies, necessity of contralateral pinning and, lastly, on the treatment and prevention of AVN and FAI to improve the outcome of all patients with SCFE.

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CHAPTER 3

Incidence and gender differences of slipped capital femoral epiphysis in the Netherlands from 1998–2010 combined with a review of the literature on the epidemiology of SCFE

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Abstract

Purpose
The incidence of slipped capital femoral epiphysis (SCFE) among children living in the Netherlands has never been published.

Methods
The national hospitalization registration system of the Netherlands was searched for the incidence of surgical procedures for SCFE in the Netherlands among different pediatric age groups between 1998 and 2010. International Classification of Diseases, 9th Revision codes was used.

Results and conclusion
The incidence of surgical procedures for SCFE during the last decade was 11.6 per 100,000 children aged 5 to 19 years. No statistical difference in the incidence of SCFE was found between boys and girls, although the incidence of SCFE did significantly increase in girls during the study period. Based on our analysis, the Netherlands appears to be the first country in which no difference in the incidence of SCFE among boys and girls has been reported. However, during the study period there has been a concomitant increase in the number of girls with SCFE.

Keywords Incidence, Slipped capital femoral epiphysis, Gender differences, The Netherlands

Introduction

Slipped capital femoral epiphysis (SCFE) is a disorder of the proximal femur that occurs mainly in peripubertal children. It is defined as the displacement of the femoral neck and shaft relative to the femoral head in the growth plate in which the proximal femoral neck and shaft move anteriorly and rotate externally relative to the femoral head, while the femoral head remains in the acetabulum. SCFE has been described as the most common hip dis-order of adolescent children in the USA [1]. Boys are more susceptible than girls in developing this disorder (Table 1). It is most often diagnosed in obese children around puberty and in children with endocrinopathies or chronic systemic diseases. In the Netherlands, the incidence of SCFE has never been published. To gain an understanding of SCFE and to compare its incidence in other countries we performed a literature search aimed at determining its incidence in different countries among children of different ages. We then performed a Dutch population-based search to determine the incidence of SCFE in the Netherlands and whether there was a difference between boys and girls. National data on body length and body weight of the children were used to interpret the findings. We compared our results with those of other studies that provide a local incidence of SCFE (Table 1).

Materials and methods

Patients

We performed a search of the national hospital registration system of the Netherlands, i.e. the "Landelijke Medische Registratie (LMR), PRISMANT kubus Ziekenhuis statistiek", which registers all patients admitted to Dutch hospitals. Only age groups and sex are listed in this registration system. Our study period covered the period 1998–2010, and the search items were the diagnosis of non-traumatic SCFE [NT SCFE; International Classification of Diseases, 9th Revision (ICD 9) code 732.2] and traumatic SCFE (T SCFE; ICD 9 code 820.01) as well as a combination of these two groups. The ICD codes only contain figures for the age categories 1–4 years, 5–9 years, 10–14 years and 15–19 years. We restricted ourselves to the age group 5–19 years. NT SCFE can be confused with T SCFE; therefore we counted the entities separately and as a combined group to these different codes. For the population figures we used Statline (Centraal Bureau voor Statistiek, the Netherlands).

Table 1.
Literature search on the incidence slipped capital femoral epiphysis

First author	Year of publication	Location of study	Incidence SCFE:100.000	Age of children enrolled in study (years)	Years of incidence noted	Male: female ratio
Henrikson [5]	1969	Gothenburg, Sweden	2.0–13.0	7–16	1947–1966	1.9
Kelsey [7]	1970	Connecticut	3.4	<25	1960–1967	2.7
			10.1	8–17		
		New Mexico	0.7	<25	1960–1967	1.7
			2.1	8–17		
Hagglund [4]	1984	Southern Sweden	61.0 (M), 30.0 (F)	5–23	1910–1982	2.3
Jerre [6]	1996	Gothenburg, Sweden	79.0	7–17	1946–1992	1.8
Loder [15]	1996	International multicenter				1.4
		study				
Noguchi [10]	2002	Japan	2.2 (M), 0.8 (F)	10–14	1997–1999	3.1
Lehmann [1]	2006	USA	10.8	9–16	1997 and 2000	1.7
Benson [2]	2008	New Mexico	6.0	8–17	1995–2006	1.9
Lim [9]	2008	Singapore	1.2	5–14	1994–2006	4.1
Murray [14]	2008	Scotland	9.7	6–18	1981–2000	1.7
Song [11]	2009	Korea	0.3	10–14	1989–2003	3.1
Larson [8]	2010	Midwestern American	8.8	9–16	1965–2005	1.8
		(Olmsted) county				
Nguyen [3]	2011	South Australia	2.8–8.2	10–19	1988–2007	1.7
Witbreuk (current study)	2012	Netherlands	11.6	5–19	1998–2010	1.1

SCFE slipped capital femoral epiphysis, *M* male, *F* female

To determine the size of the population at risk over the entire study period 1998–2010, we considered all children aged between 5 and 19 years in that period. First, we considered different age-cohorts (one cohort for each age 5, 6,…19 years) that were at risk for developing SCFE in 1998. The follow-up period for each age-cohort was defined from 1998 onwards either up to the year the patient turned 19 years old or until 2010, whichever came first. We also considered different entry-cohorts (one cohort for each year from 1999, 2000,…2010) that consisted of children who turned 5 years old in that year. For each entry-cohort, the follow-up period was

defined from the year of entry until 2010. We estimated the number of boys and girls in each cohort as the average number of boys and girls in that cohort over its follow-up period. The total number of children at risk over the period 1998–2010 was estimated by summing each estimated cohort-size (Table 2).

Statistical analysis

Incidence was defined as the population-proportion of surgical procedures for SCFE in children. The difference in the incidence rates between boys and girls was assessed by relative risks, with corresponding 95% confidence intervals (95 % CIs). The Cochran–Armitage test for trend was used to test for a linear trend of the yearly incidence rates over time. A 95 % CI not containing the value 1 or a *p* value of <0.05 was considered to be significant, while a *p* value of <0.1 was considered to be a trend. All statistical analyses were performed using SPSS ver. 15.0 (SPSS, Chicago, IL).

Results

Incidence

The total number of surgical procedures for SCFE was 609 in the period 1998–2010 for children between 5 and 19 years in the Netherlands. This translated into an incidence of 11.6 surgical procedures per 100,000 children over that period in the combined NT and T SCFE group. When the T SCFE group was not included in the analysis, the incidence of surgical procedures for NT SCFE was 8.8 per 100,000 children. The total incidence over the combined group for children aged 10–19 years was 13.7 surgical procedures per 100,000 children.

Gender ratio

In the combined group of NT and T SCFE the relative risk of exposure of boys compared to girls aged 5–19 years was 1.11 (95 % CI 0.95–1.30) over the period 1998 to 2010. The 95 % CIs over all years imply that there was no significant difference in the risk of being exposed to SCFE between boys and girls (Table 3).
The annual incidence of surgical procedures for SCFE (Fig. 1) increased significantly for girls aged between 5 and 19 years ($p = 0.034$). The incidence of the total group (boys and girls combined) did not increase significantly ($p = 0.384$) nor did the incidence for boys ($p = 0.438$).

Table 2.
Population demographic statistics for the Dutch population aged 5–19 years between 1998 and 2010

per year	5 year		6 year		7 year		8 year		9 year		10 year		11 year	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
1998	101813	96787	102743	98434	103312	98208	98589	94821	97867	93536	98602	93653	97122	93674
1999	100808	96595	102102	97076	103044	98739	103637	98518	98908	95125	98227	93922	98978	94007
2000	101584	96998	101104	96876	102363	97438	103404	99065	104015	98823	99249	95500	98575	94254
2001	99219	94823	101945	97325	101497	97188	102750	97841	103839	99401	104455	99250	99702	95887
2002	99877	94360	99469	95155	102240	97608	101826	97478	103078	98147	104224	99726	104801	99585
2003	99862	96106	99870	94451	99555	95208	102318	97765	101977	97606	103278	98292	104438	99924
2004	103353	98652	99777	95995	99817	94296	99507	95122	102244	97726	101984	97631	103317	98349
2005	104081	98997	103150	98398	99504	95779	99667	94096	99311	94933	102155	97641	101848	97489
2006	105694	101506	103707	98623	102810	98095	99230	95526	99476	93910	99078	94708	102004	97439
2007	103786	99284	105293	101149	103411	98317	102511	97821	99057	95368	99300	93753	98962	94595
2008	102861	98035	103559	99042	105151	100946	103248	98210	102381	97712	98999	95270	99306	93720
2009	102276	97540	102762	97950	103510	99013	105166	100944	103282	98191	102407	97743	99103	95345
2010	98694	94651	102325	97569	102843	97974	103609	99080	105337	101167	103381	98392	102594	97917

mean of all populations	5 year		6 year		7 year		8 year		9 year		10 year		11 year	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
1998	102931	97952	104092	99658	104786	99663	100111	96288	99333	94986	100117	95082	98906	95273
1999	101647	97309												
2000	102035	97456												
2001	99248	94852												
2002	99588	94043												
2003	99351	95617												
2004	102744	98048												
2005	103518	98455												
2006	105328	101142												
2007	103616	99105												
2008	102822	97986												
2009	102301	97555												
2010	98694	94651												
1998-2010	2693626		M											
	2573393		F											

12 year		13 year		14 year		15 year		16 year		17 year		18 year		19 year	
M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
94572	90779	93056	88625	90693	86677	91860	87542	94938	90954	97322	92256	94334	90287	95182	91565
97483	94054	94910	91143	93446	89014	91174	87067	92871	88107	95891	91525	97837	93176	94712	91571
99354	94333	97856	94410	95309	91542	94177	89467	92163	87603	93812	88633	96486	92394	98273	94457
99037	94678	99777	94716	98331	94792	96093	92029	95315	90157	93329	88241	94794	89650	97055	93852
100145	96275	99391	94996	100171	95074	98978	95238	97093	92664	96700	90942	94527	89361	95723	91162
105023	99821	100455	96491	99761	95274	100732	95463	99851	95822	98222	93285	97733	91851	95225	90727
104508	99977	105123	99933	100591	96586	99921	95389	100917	95600	100111	96025	98737	94021	98032	93100
103271	98326	104460	99889	105096	99857	100578	96586	99899	95346	100889	95719	100304	96529	98610	94923
101710	97397	103121	98211	104353	99834	104990	99784	100500	96582	99856	95461	100905	95930	100121	96913
101862	97300	101592	97251	103032	98090	104244	99775	104964	99766	100501	96587	99876	95598	100848	96329
98971	94537	101850	97282	101653	97264	103066	98101	104322	99928	105077	99894	100773	96920	100248	96397
99403	93813	99109	94637	101951	97357	101718	97350	103270	98224	104492	100129	105437	100471	101335	98101
99277	95549	99576	93992	99298	94805	102235	97580	102041	97587	103636	98488	105120	100731	106290	101715

12 year		13 year		14 year		15 year		16 year		17 year		18 year		19 year	
M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
96693	92548	95494	90451	92852	88279	93812	89019	96093	92181	97811	93296	94523	90929	95182	91565

Fig. 1.
Annual incidence of traumatic slipped capital femoral epiphysis (T SCFE) and non-traumatic SCFE (NT SCFE) for boys and girls aged 5–19 years and for the two groups combined for the period 1998–2010

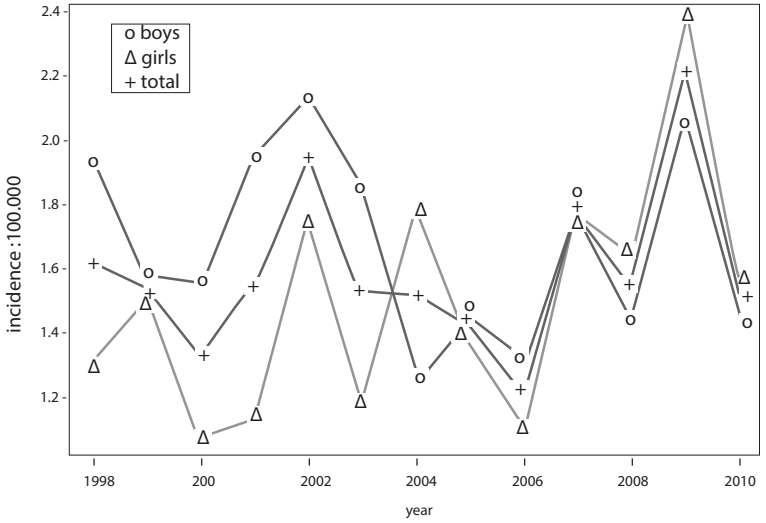


Fig. 2.
Annual incidence of NT SCFE for boys and girls aged 5–19 years and for the two groups combined for the period 1998–2010

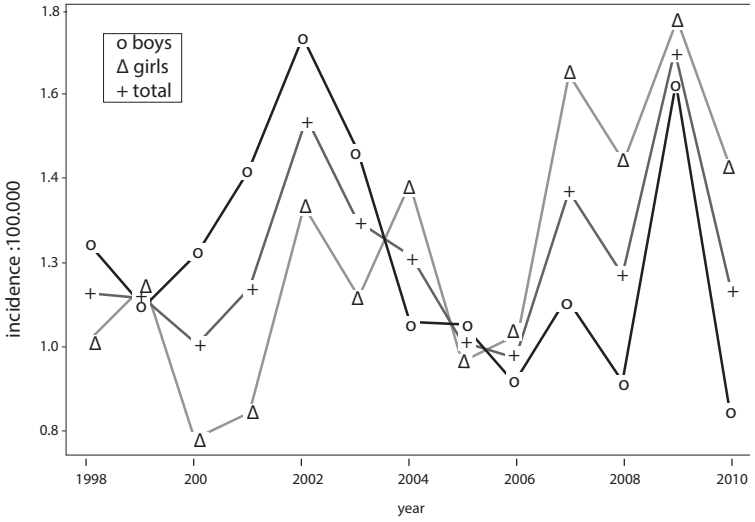


Table 3.
Relative risk of being exposed to traumatic and non-traumatic SCFE for boys compared to girls aged 5–19 years, per year and over the entire study period 1998–2010

Study year	RR [95 % CI]: M vs. F	
1998	1.49	[0.82–2.69]
1999	1.05	[0.58–1.89]
2000	1.47	[0.76–2.81]
2001	1.73	[0.94–3.19]
2002	1.22	[0.72–2.06]
2003	1.57	[0.86–2.87]
2004	0.70	[0.39–1.26]
2005	1.05	[0.57–1.93]
2006	1.20	[0.62–2.31]
2007	0.99	[0.58–1.70]
2008	0.88	[0.49–1.56]
2009	0.87	[0.54–1.41]
2010	0.91	[0.51–1.64]
1998–2010	1.11	[0.95–1.30]

RR relative risk, *CI* confidence interval

Table 4.
Relative risk of being exposed to non-traumatic SCFE for boys compared to girls aged 5–19 years, per year and over the entire study period 1998–2010

Study year	RR [95 % CI]: M vs. F	
1998	1.23	[0.61–2.47]
1999	0.96	[0.48–1.91]
2000	1.56	[0.74–3.31]
2001	1.67	[0.82–3.40]
2002	1.30	[0.72–2.36]
2003	1.31	[0.69–2.50]
2004	0.76	[0.40–1.47]
2005	1.09	[0.53–2.24]
2006	0.89	[0.43–1.85]
2007	0.68	[0.36–1.26]
2008	0.64	[0.32–1.25]
2009	0.92	[0.53–1.59]
2010	0.59	[0.30–1.18]
1998–2010	0.99	[0.82–1.18

The same results were seen in only the NT SCFE group, where the relative risk over the 13 years was 0.99 (95 % CI 0.82–1.18) (Table 4). The annual incidence of NT SCFE for girls also increased significantly ($p < 0.001$), but not for boys or the combined group ($p = 0.309$ and $p = 0.293$, respectively) (Fig. 2).

Age

In the combined NT and T SCFE group, 499 of the 609 patients (82 %) with SCFE were between 10 and 14 years of age (Fig. 3). The T SCFE group contained more boys in the age group 10–14 years, whereas the NT SCFE group contained more girls (Fig. 4). In the age group 10–14 years, the incidence rates for boys and girls did not differ significantly (relative risk 0.92, 95 % CI 0.77–1.10). In the age group 15–19 years, the incidence rates did differ: 4.3:100,000 for boys and 0.6:100,000 for girls. One possible explanation for this effect could be the earlier closure of the growth plate in girls (around 14 years of age) than in boys (around 16 years of age). In the age group 5–9 years, we observed the opposite effect: the incidence for boys was 0.6:100,000 and that for girls was 1.2:100,000.

Discussion

Our data show that the presumed gender dominance in the incidence of SCFE was not confirmed in the interval 1998–2010 in the Netherlands. The data also show an increase in the incidence of surgical procedures for SCFE in girls starting from 1998.

The strong points of this study are its nationwide coverage and the use of uniform diagnostic criteria.

One limitation to our study is our use of national Dutch hospital registration data, which did not allow us to take into account the etiology of SCFE (i.e. endocrinological, mechanical or other causes). NT SCFE is sometimes confused with T SCFE and often treated as such. Therefore, we combined the T/NT SCFE groups and also considered the NT SCFE group separately. The T SCFE group may have contained some high-energy epiphyseal fractures, leading to an overestimation of T SCFE. However, we expect this over-estimation to be very small because of the low frequency of this type of fracture in general and the low number of high-energy lesions in the Netherlands. A second limitation to our study is that the statistics did not show whether patients had a unilateral slip or a bilateral slip nor could we find information on different cultures or seasonal variations.

Fig. 3.
Percentage of patients (boys and girls combined) with NT and T SCFE divided into different age groups for the entire study period 1998–2010

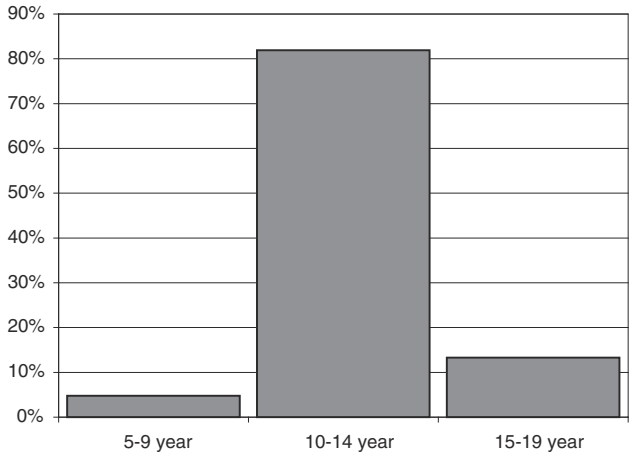
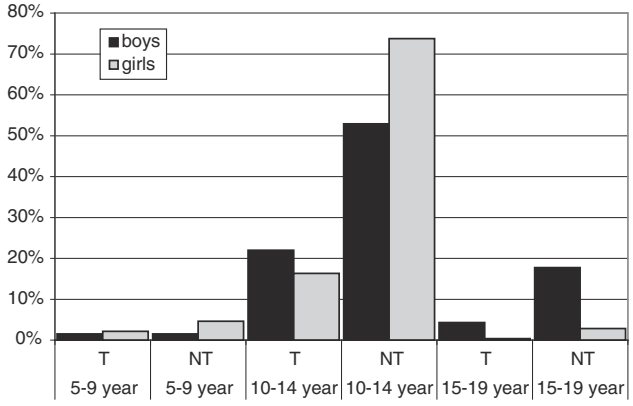


Fig. 4.
Percentage of patients with NT SCFE and T SCFE per gender and for different age groups over the entire study period 1998–2010



Incidence

It is difficult to compare the incidence we found in the Netherlands with the incidences reported in the literature because data on different age groups are presented. In addition, different estimation methods have been used. A few studies use ICD codes, as we did [1-3], but most studies used the hospital information system because this provided a defined framework [4-11]. The incidence we found is comparable to data from Sweden and the USA.

In general, it would appear that Asian countries like Japan, Singapore and Korea [9-11] have a lower incidence of SCFE than Western countries. Speculations on the reasons for these differences have focused on ethnic or nutritional differences [9,11] (see Table 1).

Gender ratio

All published studies report a male: female ratio with preponderance for boys, ranging from 1.4 to 4.1 (Singapore) [9].

Our study is unique in determining that the 95 % CIs over each of the past years in the Netherlands imply that there was no significant difference in the risk of being exposed to NT and T SCFE between boys and girls. Despite these figures, however, there has been an increase in the incidence of SCFE in girls over the past 13 years: the annual incidence increased significantly for girls aged 5 to 19 years. The incidence for boys did not increase significantly nor did that for the combined group.

Figure 1 show that the difference is small between girls and boys on an annual basis but that over the years of the study period there was an increase in the incidence of SCFE in girls compared to boys. To date, our study is the first to report such a difference at the national level while concomitantly describing an increase in the incidence of SCFE in girls over the last decade.

A decrease of male predominance has also been found in Japan and Sweden. Despite the low incidence in Japan, a fivefold increase in boys and tenfold increase in girls were found between 1974 and 1999 [10]. In Sweden, the pre-dominance of boys has decreased from 85–90 to 60–65 % during the first decade of this century [4, 12].

Age

We found the same distribution of children with SCFE in different age groups as reported in the other studies. All studies describe a peak in incidence around the age of onset of puberty. In our group, the 609 patients with SCFE were divided as follows: 5 % (29) in the 5- to 9-year-old group, 82 % (499) in the 10- to 14-year-old group and 13 % (81) in the 15- to 19-year-old group (see Fig. 3). A majority of studies describe a decrease in the mean age of onset during recent years. Hagglund et al. [4] suggest that the decreasing age at onset of SCFE is probably caused by the onset of puberty at an earlier age during the last century and by the increased awareness of parents, the social environment and physicians, leading to an earlier diagnosis of SCFE.

Body length

In the Netherlands nation-wide growth studies have been conducted since 1955. The fifth Dutch Growth study was carried out between 2008 and 2010. These results can be compared to earlier studies in the Netherlands. Schonbeck et al. [13] report that there has been no increase in the body length of boys and girls between 1997 and 2009 in the Netherlands.

Body weight

Figures obtained from the Factsheet Results Fifth National Growth Study TNO (June 10, 2010) show that there has been a trend for an increase in overweight and obesity from 1997 to 2009. A comparison of data for the period 1997–2009 shows that 9.4 versus 13.3 % of Dutch boys and 11.9 versus 14.9 % of Dutch girls aged 2–21 years were overweight and 0.9 versus 1.8 % of the boys and 1.6 versus 2.2 % of the girls were classified as obese [13]. Although the boys have increased in body weight more than the girls, the incidence of SCFE for boys—but not for girls—seems to have stabilized. The increase of SCFE in girls in the past decade may also be due to these increases in body weight, but we have no data to support such a hypothesis for boys. Increasing obesity in adolescents has been found in many different countries, as has an increase in SCFE [2, 10, 11, 14]. In major cities in the Netherlands overweight prevalence has stabilized, with no increase in the body mass index, which leads to the hope that the rising trend in overweight is starting to turn [13].

Conclusion

Based on the results of our study, in the Netherlands there was no difference in the incidence of surgical procedures for SCFE between boys and girls during the period 1998–2010. In the past 13 years there has been an increase in the incidence of surgical procedures for SCFE among girls in the combined NT/T SCFE group and in the NT SCFE group alone. The incidence in boys and in the combined group has not increased. From other national registries we know that there has been an increase in the number of Dutch children who suffer from overweight and obesity, while the body length has not increased the past 10 years.
The incidence determined in our study seems to be comparable with that of other Western countries such as the USA and Sweden.

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CHAPTER 4

Slipped capital femoral epiphysis and its association with endocrine, metabolic and chronic diseases: a systematic review of the literature

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Abstract

Purpose

Puberty, obesity, endocrine and chronic systemic diseases are known to be associated with slipped capital femoral epiphysis (SCFE). The mechanical insufficiency of the physis in SCFE is thought to be the result of an abnormal weakening of the physis. However, the mechanism at the cellular level has not been unravelled up to now.

Methods

To understand the pathophysiology of endocrine and metabolic factors acting on the physis, we performed a systematic review focusing on published studies reporting on hormonal, morphological and cellular abnormalities of the physis in children with SCFE. In addition, we looked for studies of the effects of endocrinopathies on the human physis which can lead to cause SCFE and focused in detail on hormonal signaling, hormone receptor expression and extracellular matrix (ECM) composition of the physis. We searched in the PubMed, EMBASE.com and The Cochrane Library (via Wiley) databases from inception to 11th September 2012. The search generated a total of 689 references: 382 in PubMed, 232 in EMBASE.com and 75 in The Cochrane Library. After removing duplicate papers, 525 papers remained. Of these, 119 were selected based on titles and abstracts. After excluding 63 papers not related to the human physis, 56 papers were included in this review.

Results

Activation of the gonadal axis and the subsequent augmentation of the activity of the growth hormone–insulin-like growth factor 1 (GH-IGF-1) axis are important for the pubertal growth spurt, as well as for cessation of the physis at the end of puberty. The effects of leptin, thyroid hormone and corticosteroids on linear growth and on the physis are also discussed. Children with chronic diseases suffer from inflammation, acidosis and malnutrition. These consequences of chronic diseases affect the GH-IGF-1 axis, thereby, increasing the risk of the development of SCFE. The risk of SCFE and avascular necrosis in children with chronic renal insufficiency, growth hormone treatment and renal osteodystrophy remains equivocal.

Conclusions
SCFE is most likely the result of a multifactorial event during adolescence when height and weight increase dramatically and the delicate balance between the various hormonal equilibria can be disturbed. Up to now, there are no screening or diagnostic tests available to predict patients at risk.

Keywords Slipped capital femoral epiphysis; Systematic review; Endocrine, metabolic and chronic diseases

Abbreviations

AR	Androgen receptor
CRF	Chronic renal failure
ECM	Extracellular matrix
ER	Estrogen receptor
GC	Glucocorticoids
GH	Growth hormone
IGF-1	Insulin-like growth factor 1
IGF-1R	Insulin-like growth factor 1 receptor
IGFBP3	Insulin-like growth factor binding protein 3
IHH	Indian hedgehog
IHH–PTHrH	Indian hedgehog–parathyroid hormone-related hormone
LH	Luteinising hormone
MMP	Matrix metalloproteinases
MMP13	Matrix metalloproteinase 13
MMP9	Matrix metalloproteinase 9
PTH	Parathyroid hormone
rhGH	Recombinant human growth hormone
ROD	Renal osteodystrophy
SCFE	Slipped capital femoral epiphysis
T3	Triiodothyronine
T4	Thyroxine

Introduction

Slipped capital femoral epiphysis (SCFE) is a disorder of the proximal femur in adolescents. SCFE is defined as the displacement of the femoral head relative to the femoral neck and shaft in the physis. The proximal femoral neck and shaft move anteriorly and rotate externally relative to the femoral head, leaving the femoral head stabilized in the acetabulum. SCFE is most often diagnosed in obese adolescents and in children with endocrinopathies or chronic systemic diseases. The pathogenesis of SCFE has not been unravelled fully so far. A precise insight into the pathogenesis of SCFE is important for understanding the disease and possible development of rational therapy.

It is thought that SCFE is the result of mechanical insufficiency of the proximal femoral physis. The slip is a result of either an abnormally high load across a normal physis or a physiological load across an abnormally weak physis, or a combination of these two. Mechanical factors for an abnormally high load include obesity, femoral retroversion and increased physeal obliquity [1]. The majority of adolescents with SCFE might not have hormonal metabolic or chronic diseases, but they are obese and fast growing. However, it seems unlikely that mechanical overload of the proximal femur epiphysis, by, for example, high body weight only, can lead to SCFE. Many children in their growing age are exposed to high mechanical loads of their hip joints during normal activities and sports activities for example.

Conditions that weaken the physis include endocrine or systemic diseases, for example, hypothyroidism, growth hormone suppletion and hypogonadal abnormalities [1].

The underlying mechanisms that are involved in the development of abnormal weakening of the physis may originate from the cellular level and include dysregulation of chondrocytes in the hypertrophic layer of the physis, as well as disturbances in the extracellular matrix (ECM) turnover. In addition, these phenomena may result from improper or dysregulated signaling through the several pathways involved, for instance, hormonal receptors or its second messengers.

However, how metabolic and endocrine factors can cause a weak physis is unclear. In order to obtain insight into the available data on the role of metabolic and endocrine factors in physis weakening and the pathogenesis of SCFE, we performed a systematic review with emphasis on the pathogenetic mechanisms. In this review, we will only discuss the association of endocrine, metabolic and

chronic diseases and SCFE. The role of anatomical factors related to SCFE is not the subject of this review.

Methods

Literature search

We performed systematic searches in the databases Pub-Med, EMBASE.com and The Cochrane Library (via Wiley) from inception to 11th September 2012. Search terms included controlled terms from MeSH in PubMed and EMtree in EMBASE.com, as well as free-text terms. We used free-text terms only in The Cochrane Library. Search terms expressing 'epiphysiolysis' were used, in combination with search terms comprising 'endocrine diseases' or 'biopsy'. The search was then combined with terms for 'extracellular matrix proteins, hormones' and filtered for 'children' (Table 1). The references of the identified articles were searched for relevant publications.

Selection phase

Two reviewers (M.M.W. and E.P.J.) independently screened all potentially relevant titles and abstracts for eligibility. If necessary, the full-text article was checked for the eligibility criteria. Differences in judgment were resolved through a consensus procedure. Studies were included if they met the following criteria: studies discussing the histology of biopsies in SCFE physis, evaluation of hormonal factors influencing the human physis, SCFE and the ECM in the human physis. Exclusion criteria were articles not related to the human physis, animal-related research on the physis and drugs-related studies. The full text of articles was obtained for further review.

Table 1.
Search strategy in PubMed up to 11th September 2012 (to be read from the bottom up)

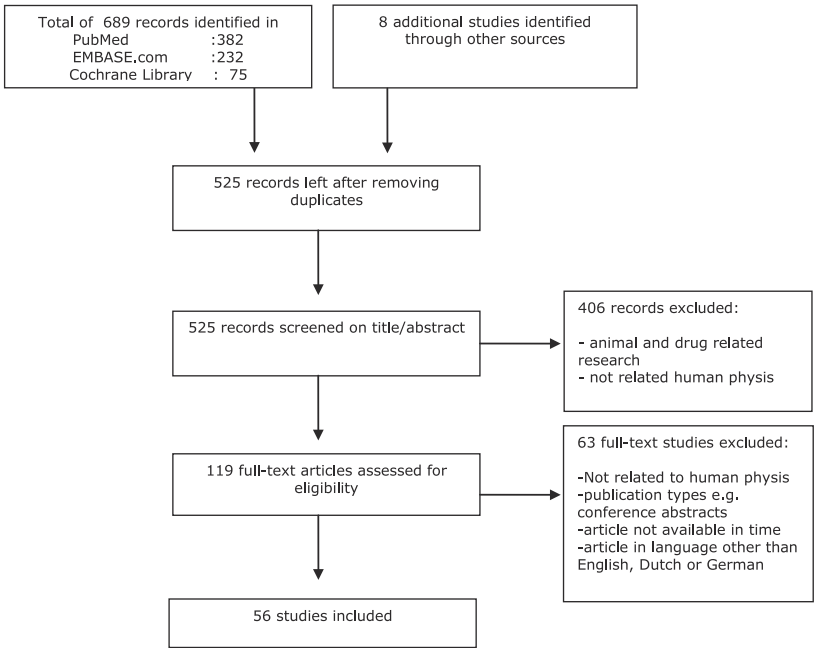
Set	Search terms	No. of results
#6	#1 AND (#2 OR #3) AND #4 AND #5 NOT (animals[mh] NOT humans[mh])	382
#5	child*[tw] OR schoolchild*[tw] OR adolescen*[tw] OR pediatri*[tw] OR paediatr*[tw] OR boy[tw] OR boys[tw] OR boyhood[tw] OR girl[tw] OR girls[tw] OR girlhood[tw] OR youth[tw] OR youths[tw] OR teen[tw] OR teens[tw] OR teenager*[tw] OR puberty[tw]	2,601,373
#4	"Extracellular Matrix Proteins"[Mesh] OR "Collagen Type II"[Mesh] OR "Collagen Type IX"[Mesh] OR "Collagen Type X"[Mesh] OR collagen[tiab] OR "Aggrecans"[Mesh] OR aggrecan[tiab] OR "Aggrecans"[tiab] OR "Proteoglycan Core Proteins"[tiab] OR "SOX9 Transcription Factor"[Mesh] OR "SOX9"[tiab] OR "SOX 9"[tiab] OR "Matrix Metalloproteinase 9"[Mesh] OR "Matrix Metalloproteinase 9"[tiab] OR MMP9[tiab] OR "92 kDa Gelatinase"[tiab] OR "92 kDa Type IV"[tiab] OR "Matrix Metalloproteinase 13"[Mesh] OR "metalloproteinase 13"[tiab] OR "Metalloproteinase-13"[tiab] OR "matrixmetalloproteinase 13"[tiab] OR "matrix metalloproteinase thirteen"[tiab] OR "matrixmetalloproteinase thirteen"[tiab] OR mmp13[tiab] OR "mmp 13"[tiab] OR "MMP-13"[tiab] OR "Collagenase- 3"[tiab] OR "Collagenase 3"[tiab] OR "Insulin-Like Growth Factor I"[Mesh] OR "Insulin-Like Growth Factor I"[tiab] OR "IGF I"[tiab] OR "IGF-I"[tiab] OR "Bone Morphogenetic Proteins"[Mesh] OR "Bone Morphogenetic Proteins"[tiab] OR "Bone Morphogenetic Protein"[tiab] OR BMP*[tiab] OR "physeal architecture"[tiab] OR "Estrogens"[Mesh] OR Estrogen*[tiab] OR oestrogen*[tiab] OR "Testosterone"[Mesh] OR Testosteron*[tiab] OR "Leptin"[Mesh] OR Leptin[tiab] OR "Ghrelin"[Mesh] OR Ghrelin[tiab] OR "Triiodothyronine"[Mesh] OR "T3 TRa1"[tiab] OR b1[tiab] OR "beta-1"[tiab] OR "T3 Thyroid Hormone"[tiab] OR "Thyroxine"[Mesh] OR "T4 Thyroid Hormone"[tiab] OR IGFI[tiab] OR IGF1[tiab] OR "IGF 1"[tiab] OR "Receptor, IGF Type 1"[Mesh] OR IGF1R[tiab] OR "Insulin-Like Growth Factor II"[Mesh] OR "Insulin-Like Growth Factor II"[tiab] OR "IGF II"[tiab] OR "IGF-II"[tiab] OR IGFII[tiab] OR IGF2[tiab] OR "IGF 2"[tiab] OR "Receptor, IGF Type 2"[Mesh] OR IGF2R[tiab] OR "Insulin-Like Growth Factor Binding Proteins"[Mesh] OR IGFBP[tiab] OR sox[tiab] OR immunoglobin[tiab] OR "C3 protein, human"[Supplementary Concept] OR C3[tiab]	603,352
#3	"Biopsy"[Mesh] OR "Microscopy, Electron"[Mesh] OR "Microdissection"[Mesh] OR ((microdissection[tiab] OR micro- dissection[tiab] OR Biopsy[tiab] OR biopsies[tiab] OR "electron microscopy"[tiab] OR "TEM"[tiab]) NOT medline[sb])	537,806
#2	"Growth Disorders"[Mesh] OR "growth disorder"[tiab] OR "growth disorders"[tiab] OR "Hypothyroidism"[Mesh] OR "Hypothyroidism"[tiab] OR "Hypothyroidisms"[tiab] OR "Hypoparathyroidism"[Mesh] OR "Hypoparathyroidism" [tiab] OR "Hypoparathyroidisms" [tiab OR "Hyperparathyroidism" [Mesh] OR "Hyperparathyroidism" [tiab] OR "Hyperparathyroidisms" [tiab] OR "Renal Osteodystrophy" [Mesh] OR "Renal Osteodystrophy" [tiab] OR "Renal Osteodystrophies" [tiab] OR "Renal Insufficiency" [Mesh] OR "Renal Insufficiency"[tiab] OR "Renal Insufficiencies"[tiab] OR "Renal failure"[tiab] OR "Renal failures"[tiab] OR "kidney failure"[tiab] OR "kidney failures"[tiab] OR "Growth Hormone"[Mesh] OR "Growth Hormone"[tiab] OR GH[tiab] OR somatotropin*[tiab]	295,106
#1	"Epiphyses, Slipped"[Mesh] OR epiphysiolysis[tiab] OR epiphysiolyses[tiab] OR SCFE[tiab] OR "Growth Plate"[Mesh] OR "Epiphyses"[Mesh] OR epiphyses[tiab] OR epiphysis[tiab] OR "Growth Plate"[tiab] OR "Epiphyseal plate"[tiab] OR "Epiphyseal plates" [tiab] OR "Epiphyseal cartilage" [tiab] OR "Epiphyseal cartilages" [tiab] OR "Extracellular Matrix" [Mesh] OR "Extracellular Matrix" [tiab] OR "Extra cellular Matrix" [tiab] OR "ECM" [tiab]	87,886

Results

The literature search generated a total of 689 references: 382 in PubMed, 232 in EMBASE.com and 75 in The Cochrane Library. Another eight additional studies identified through other sources were included.

After removing duplicates of references that were selected from more than one database, 525 papers remained. Of these, 119 papers were selected based on titles and abstracts. Sixty-three papers were excluded after judgment if not related to human biology, publication types, e.g. conference abstracts, article not available in time or article written in a language other than English, Dutch or German. Fifty-six papers were included in this review. The flow chart of the search and selection process is presented in Fig. 1.

Fig. 1.
Flow chart of the search and selection procedure of studies



For this review, we present the results under five headings:

The physis in SCFE: reviews studies specifically dealing with SCFE
Endocrinology of growth and puberty: reviews the major endocrine effects on the physis throughout puberty
- Obesity and SCFE
  - GH-IGF-1 axis and SCFE
  - Sex steroids in puberty and SCFE
  - Leptin and SCFE
- Thyroid hormones and SCFE
- Glucocorticoids and SCFE

Vitamin D: reviews the effects of vitamin D at the growth plate
Chronic disease: reviews the effects of chronic disorders on the physis
Diagnostic endocrine measurements in SCFE: reviews the studies that specifically investigated SCFE

The physis in SCFE

Histological changes in SCFE

Histological studies of tissue obtained from biopsies during surgery for SCFE show some characteristic features of the physis.
Changes in the longitudinal orientation of the cartilage cells of the physis, which are normally parallel to the axis of the bone, are seen in tissues taken from biopsies in SCFE. In SCFE, pathologic tangential forces damage the hypertrophic cartilage. As a result of the longitudinal orientation of these fibres, this zone is the least protected from these shearing forces [2]. However, it is not always clear as to whether the observed changes in cell orientation are found before or after the SCFE occurred. Obviously, the actual time of biopsies was taken after the slip occurred.
The resting zones of the epiphysis appeared to be relatively normal in SCFE [3-6], although some tissue samples showed clusters of numerous chondrocytes cells [5].
The proliferative and hypertrophic zones of the epiphysis in SCFE were widened compared with normal physis, and showed irregular columnar organization with gradual loss of longitudinal septa and diminished number of chondrocytes in each column [3-7]. Interestingly, Adamczyk et al. showed that apoptosis was increased throughout the physis in SCFE, in contrast with controls, where apoptosis was

found only in the hypertrophic zone [8]. The chondrocytes showed intracellular abnormalities [5, 7, 9]. An increase in the nuclear and cytoplasmic density was seen in the proliferative and hypertrophic chondrocytes with SCFE and an increase in cytoplasmic glycogen [7, 9]. Other investigators, however, could not confirm these findings [3, 6].

The ECM of the physis had abnormal longitudinal septa with deficiency in collagen [3, 5, 7, 9]. The amount of proteoglycans in the ECM was moderately decreased in the matrix of the physis in SCFE compared to normal [3, 7, 9]. Also, abnormal proteoglycans were found [5]. Matrix vesicles, secreted by hypertrophic chondrocytes, were more abundant than in the controls [5, 7, 9]. Matrix vesicles contain calcium phosphates, hydroxyapatite and matrix metalloproteinases (MMP). The contents of these vesicles change the structure of the ECM and begin the process of calcification of the matrix [10]. Lacunar spaces in the hypertrophic zones were seen, with reactive changes showing callus formation [3, 4, 6].

Scharschmidt et al. performed laser capture microdissection followed by quantitative reverse transcription-polymerase chain reaction analysis of mRNA on the physis tissue of SCFE obtained by biopsies. They observed down-regulation of both type 2 collagen and aggrecan in physes of patients with SCFE [11].

In conclusion, the physis in SCFE shows many histological differences compared to the normal physis in columnar organisation, on the cellular level and in the ECM. The fundamental problem is that the role of the described changes is unknown. It is unclear as to whether they are causal or adaptive. Some of these changes can occur also in endocrine or metabolic abnormalities, as will be discussed further in this review (see Figs. 2 and 3).

Endocrinology of growth and puberty

During the pubertal growth spurt, endocrine changes are enormous. Disturbances of the endocrine mechanisms may lead to weakening of the physis of the proximal femur. Before puberty, the major endocrine factors involved in linear growth and skeletal development are the growth hormone–insulin-like growth factor 1 (GH-IGF-1) axis and triiodothyronine (T3).

With the onset of puberty, the gonadal axis is reactivated after years of quiescence. Increasing levels of sex hormones are responsible for an augmentation of the GH-IGF-1 axis activity.

Sex hormones, growth hormone, IGF-1 as well as other endocrine, paracrine and autocrine factors exert a direct and indirect effect on the physis [12-14].

Since obesity and pubertal growth spurt seem to be the main risk factors for SCFE, we will start by explaining the influence of (1) the GH-IGF-1 axis, (2) sex steroids and (3) leptin. Their influence on the physis is complex. Subsequently, we will discuss thyroid hormone, glucocorticoids, vitamin D, chronic disease and diagnostic endocrine measurements in SCFE.

Obesity and SCFE

GH-IGF-1 axis and SCFE Growth hormone (GH) is a peptide hormone that stimulates growth, cell reproduction and regeneration in humans and other animals. GH is normally produced in an abundant quantity by the pituitary somatotroph cells. It is secreted in a pulsatile manner stimulated by hypothalamic GH-releasing hormone (GHrH), inhibited by somatostatin (growth hormone-inhibiting hormone) and under negative feedback of the peripheral effectors GH, IGF-1 and insulin-like growth factor binding protein (IGFBP) [15-18]. During pubertal development, the basal secretion and pulse amplitude of GH increases two-fold to three-fold as a result of increasing levels of sex hormones [12].

According to the dual effector theory, GH can act directly as well as indirectly, via IGF-1, on the physis. Directly, GH acts on the resting zone and is responsible for local IGF-1 production, which stimulates clonal expansion of proliferative chondrocytes in an autocrine/paracrine manner. Indirectly, GH stimulates IGF-1 synthesis in the liver, which, in turn, activates chondrocyte proliferation in the physis [12, 18-23].

IGF-1 is a peptide hormone and a major metabolic regulator in the body. Most circulating IGF-1 is synthesized by the liver. It has anabolic effects on muscle and bone and catabolic effects on fat [16]. Recent studies indicate that locally acting IGF-1 is a key determinant of endochondral ossification and that GH, glucocorticoids (GC) and T3 regulate the expression of IGF-1 and its receptor in the physis directly [14, 22]. Insulin like growth factor 1 (IGF-1) gives thanks to its name from the similarity of insulin. It also explains the ability of IGF-1 to bind to insulin receptors and insulin's ability to bind to the IGF-1 receptor [17, 18].

Hepatic IGF-1 is almost entirely bound to IGFBPs. There is a family of six, of which IGFBP3 is the most important. Acid labile subunit (ALS), also synthesized by the liver, acts as a stabilizer for the ternary complex with IGF-1 and IGFBP3. Only 1 % of plasma IGF-1 occurs in free bioactive form [13, 15, 17, 24]. Circulatory IGF is detected by the hypothalamus and pituitary gland to inhibit GH secretion, completing the feedback loop [16].

Fig. 2.
Normal physis of a 2-year-old boy after amputation for tibial aplasia. At the top is the regularly organized cartilage of the growth plate, with the different zones leading at the bottom to the ossification zone

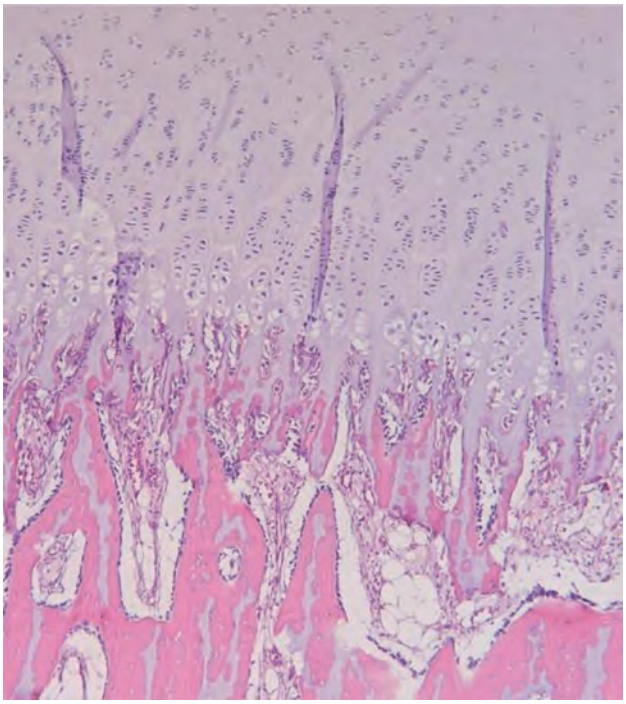
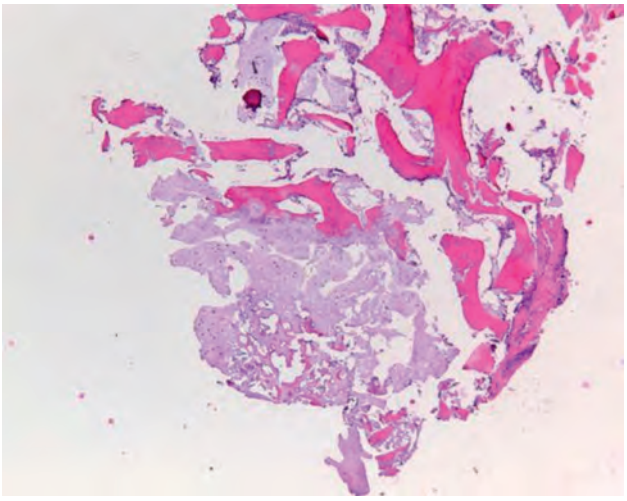


Fig. 3.
Abnormal physis taken of a 10-year-old boy with slipped capital femoral epiphysis (SCFE) on both sides. At the top-right of the image, the ossification is visible, and at the bottom, the disorganized cartilage from the growth plate is visible. The normal regular organisation is lacking



In the largest US registry, the National Cooperative Growth Study (NCGS), the use of recombinant human growth hormone (rhGH) treatment in children with short stature did not appear to measurably increase the risk for SCFE [25]. There are hardly any data to determine the role of abnormalities in this axis in SCFE.
In conclusion, the GH-IGF-1 axis is a major growth regulator throughout childhood and adolescence, has direct and indirect influence on the physis and is regulated by different hormones and growth factors itself.

Sex steroids in puberty and SCFE The androgen testosterone and the oestrogen estradiol are the main steroid hormones that are produced by the testes and ovaries, respectively. Androgens can be converted to oestrogens in other tissues such as liver, fat or muscle, which is especially important in overweight boys and men. In addition to the gonads, the adrenal glands produce androgens that have a low androgen activity compared to testosterone.
Androgens and oestrogens are responsible for the pubertal growth spurt. The subsequent closure of physis is dependent on oestrogens in females as well as in males [14, 20]. The onset of the adolescent growth spurt is 2 years earlier in girls than in boys. A longer period of prepubertal growth as well as a higher growth spurt account for the greater adult height of males compared to females [17]. Not surprisingly, SCFE also occurs in an earlier phase in girls, with an average age of 12.0 years, than in boys, with an average age of 13.5 years [1].
Androgens and oestrogens have a direct growth-stimulating effect on the physis, as well as an indirect effect through the enhancement of GH secretion from the pituitary gland mediated by estrogen receptor (ER-α). Thus, androgens can only influence the GH-IGF-1 axis after aromatisation into oestrogens [12, 13, 18, 26, 27]. Boys have aromatase activity in numerous tissues, including adipose tissue and muscle. Boys with idiopathic gynaecomastia are generally characterized by relative obesity, resulting in increased conversion of androgens to oestrogens [20]. Boys with the rare condition of aromatase excess syndrome have increased conversion of testosterone to estradiol and, typically, develop gynaecomastia as well as increased longitudinal growth. In contrast, delayed skeletal maturation and low bone mineral density are observed in patients with aromatase deficiency and oestrogen receptor resistance [28], underlining the importance of oestrogen action in skeletal maturation, epiphyseal closure and bone mass accrual.
Oestrogens are, thus, important in the regulation of linear growth of both sexes. In addition, oestrogens have a direct and an indirect role on the physis. Directly,

oestrogens stimulate the local production of IGF-1 and other growth factors. Indirectly, low concentrations of oestrogens stimulate GH secretion, thereby, increasing circulating IGF-1 levels that, in turn, stimulate chondrocyte growth in the proliferation zone and may also potentiate clonal expansion. Oestrogens also seem to have a biphasic effect on the physis. Low concentrations of oestrogen augment skeletal growth, whereas continued high levels of oestrogens lead to epiphyseal fusion. High doses of oestrogen inhibit clonal expansion and cell proliferation in the hypertrophic zone. Furthermore, high concentrations of oestrogen induce apoptosis of hypertrophic chondrocytes and stimulate osteoblast invasion in the physis [12, 18, 20, 26].

The current understanding of how oestrogens affect growth may suggest separate roles for the different estrogen receptors (ERs). Two ERs exist: ER-α and ER-β. Juul et al. [20] found that ER-α is localized in all zones of the physis and ER-β is expressed in hypertrophic chondrocytes exclusively. Nilsson et al. [29] demonstrated that both receptors are present in all zones of the physis, but in a greater frequency in the resting and proliferative zones. The androgen receptor (AR) was found to be more abundant in the resting and hypertrophic zones.

Also, a new membrane-bound ER G-protein-coupled receptor 30 (GPR30) was discovered. The highest level of this receptor was found in hypertrophic chondrocytes. The receptor revealed a weak immunostaining in the resting zone. During puberty, a decline was found in the expression of this receptor in both boys and girls. This new receptor could play an important role for the cessation of growth in puberty [30].

Testosterone has, not only after aromatisation, an effect on growth but also directly on the physis by the stimulation of proliferation and differentiation in chondrocytes. This direct effect on the human physis is not necessary for the pubertal growth acceleration or for the cessation of growth. ARs have been found in hypertrophic chondrocytes in the human physis and cartilage. Some organs are capable of synthesizing sex steroids from sulphated precursors which are present in high amounts in the circulation. The term 'intracrinology' was introduced, suggesting that sex steroids can be synthesized locally and act in the same cell without being released, indicating that a more complicated mechanism may be available in the physis [12, 13, 18, 29].

Delayed sexual maturation is often present in patients with SCFE, which might suggest a delay in closure of the physis. This creates a prolonged phase of weakness that makes the physis vulnerable for the effects of increasing load, mainly in the

pre-existence of obesity. This delay can, thus, be involved in the slip of the epiphysis in SCFE and most children with this condition are, indeed, obese [1, 31].

Leptin and SCFE Leptin is a protein hormone that plays a key role in regulating energy intake and energy expenditure. It is secreted mostly in the adipocytes of white adipose tissue. The level of circulating leptin is proportional to the total amount of fat in the body [13, 32]. In obese children, leptin levels are in direct proportion to the increase in body mass index (BMI) [13].
Leptin plays a permissive role in the onset of puberty and in pubertal growth. Leptin has a direct effect on the physis through leptin receptors and induces an increase in the width of the proliferative zone in a dose-dependent manner. This leads to the enhancement of proliferation and differentiation of the chondrocytes in the physis [12, 32]. Interestingly, in many patients with SCFE, an increase in the width of the proliferative and hypertrophic zones has been found [3-7]. Leptin has synergistic effects with the GH-IGF axis [12, 13] as a skeletal growth factor that, independent of the presence of GH, stimulates IGF-1 and IGF-1 receptor gene expression, indicating that a relation exists between mechanisms regulating weight and mechanisms regulating linear growth. Most likely, there are many links between leptin, adipocytes, GH, thyroxine, IGF-1 and chondrocytes, but the precise nature of these interactions is incompletely understood [32].
In obese children, serum GH levels are usually low. Indirect growth effects in obese children may not be induced by leptin but mediated by insulin. Obesity leads to insulin resistance and, thereby, to an increase of insulin blood levels. Insulin, an anabolic hormone, can, to a certain extent, promote growth as a result of the resemblance of the insulin and IGF-1 receptors. Insulin in high levels may bind to and activate the IGF-1 receptor. Furthermore, insulin may also stimulate accelerated growth by decreasing IGFBP-1, which leads to an increase of free IGF-1 and, consequently, in its biological activity [13].
In conclusion, SCFE is found more often in overweight children [31]. In obese children, leptin levels are increased. Leptin can cause an increase in the width of the proliferative zone, as has been found in SCFE.

Thyroid hormones and SCFE
Triiodothyronine (T3) and thyroxin (T4) are tyrosine-based hormones, produced by the thyroid gland, that are primarily responsible for regulation of the metabolism. Thyroid hormones are regulated by thyroid-stimulating hormone (TSH) by the

anterior pituitary gland and thyroid-releasing hormone (TRH) by the hypothalamus. Thyroid hormones are essential for longitudinal growth and normal skeletal maturation [12].

Circulating active thyroid hormone, T3, is formed by deionisation of T4 in the liver and kidney. T4 is derived from the thyroid gland [33].

T3 is essential for resting zone cells differentiation and hypertrophic chondrocyte differentiation during bone formation. T3 has an indirect role on growth by influencing GH secretion and a direct role which has been shown by the presence of thyroid receptor α1 (TRα1) and thyroid receptor β (TRβ) presence in proliferating chondrocytes in the physis. T3 also regulates osteoblast activity, bone turnover and vascular invasion [14, 17, 18, 32, 33].

Tightly controlled concentrations are essential [14, 33]: childhood hypothyroidism causes growth failure, whereas thyrotoxicosis causes accelerated growth and slightly advanced bone age, which may lead to a moderately decreased final height.

The negative feedback loop of an important regulator of chondrocyte differentiation, Indian hedgehog–parathyroid hormone-related hormone (IHH–PTHrH), can be altered by the thyroid status. IHH belongs to a family of hedgehog proteins which plays a crucial role in embryonic development. IHH is secreted by pre-hypertrophic chondrocytes and is mainly a regulator of the pace of chondrocyte differentiation. It stimulates the local production of PTHrP. PTHrP acts on PTHrP receptor expressing pre-hypertrophic chondrocytes to maintain cell proliferation, reduce IHH production and complete a feedback loop in which PTHrP exerts a negative signal that inhibits hypertrophic differentiation [18, 33, 34]. The levels of expression in early hypertrophic chondrocytes of IHH and PTHrP are higher during early puberty than at later stages. It has been suggested that these proteins might be involved in the regulation of pubertal growth because a reduced expression of IHH–PTHrH is found during the progress of pubertal development [35]. The IHH–PTHrH feedback loop does not only regulate chondrocyte proliferation and differentiation but also osteoblast differentiation, thereby, coupling chondrogenesis to osteogenesis [18, 36].

In conclusion, thyroid hormone exerts direct and indirect effects on the physis and facilitates physis closure at the end of puberty via signaling of the IHH–PTHrH pathway. As SCFE occurs at the end of puberty, where the closure of the physis is delayed, it could be possible that changes in thyroid hormones disturb the closure of the physis. Although there are hardly data available to determine the exact role of abnormalities in this axis in SCFE, Wells et al. [37] found that this was the most

frequent abnormality in SCFE (see section "Diagnostic endocrine measurements in SCFE").

Glucocorticoids and SCFE

Glucocorticoids (GC) are steroid hormones that are produced in the adrenal cortex. This production is regulated by adrenocorticotropic hormone (ACTH) by the anterior pituitary gland and corticotrophin-releasing hormone (CRH) by the hypothalamus. Synthetic analogues of these hormones are widely used in the treatment of a variety of diseases. Mineralocorticoids are also produced by the adrenal gland but are not discussed in this review.

GC in physiological concentration facilitate normal growth, whilst in excess, GC suppress physis chondrocyte proliferation, induces prolonged resting period and reduces matrix synthesis with increased apoptosis. These effects are induced indirectly by alterations of the GH-IGH-1 axis and directly by local effects through GC receptors that are expressed in the physis [14, 18, 38-40]. Furthermore, GC inhibits the sulphation of cartilage matrix, mineralization of new bone, osteoblast activity and stimulates bone resorption [22, 38, 40].

Long-term high GC concentrations cause growth retardation and osteoporosis. GC alters pulsatility and diminishes the secretion of GH from the pituitary through an elevation of hypothalamic somatostatin release. In addition, GC causes end-organ-insensitivity to the GH-IGF-1 axis by reducing expression of the GH and IGF-1 receptor in the physis. Furthermore, GC has direct effects on the growth plate mediated by the GC receptor, for example, increased apoptosis in the physis [14, 38-40]. The effects depend on the GC concentration used and the duration of exposure. GC growth-depressing effects may be partially counterbalanced by GH treatment [18, 40].

In conclusion, GC, mainly in long-term high concentrations, has negative effects on growth by direct and indirect mechanisms. The relation between SCFE and GC has not been yet demonstrated.

Vitamin D

Vitamin D is a group of fat-soluble steroids responsible for the intestinal absorption of calcium and phosphate. Vitamin D can be ingested as cholecalciferol or ergocalciferol and it can also be synthesized (from cholesterol) by sun exposure. In the liver, vitamin D is converted to calcidiol. Part of the calcidiol is converted

in the kidneys to calcitriol (1,25-dihydroxycholecalciferol), the biologically active form of vitamin D. Calcitriol circulates as a hormone in the blood, regulating the concentration of calcium and phosphate in the bloodstream and promoting growth, mineralization and remodeling of bone.

Calcitriol has a direct action on epiphyseal chondrocytes. They stimulate cell growth in a dose-dependent, biphasic manner: proliferation is stimulated at low concentrations and inhibited by high concentrations. Also, it has synergetic effects with PTH on chondrocyte proliferation. A possible link between IGF and calcitriol has been described by showing an increased expression of IGF-1 receptor and/or local IGF-1 synthesis [21, 41]. Accelerated growth after the treatment of nutritional vitamin D, in vitamin-D-deficient patients, is mediated through activation of the GH-IGF1 system and suggests an important role of vitamin D as a link between the proliferating cartilage cells of the growth plate and GH-IGF1 secretion [41].

In the literature, an association has been described between seasonal variation and SCFE. This might be related to a decrease of vitamin D [42].

Chronic disease

Growth failure is a distinctive feature in children with chronic diseases. Some children with chronic diseases can suffer from inflammation, malnutrition and metabolic acidosis, which may result in abnormal GH-IGF-1 axis activity [43].

Chronic disease caused by inflammatory processes may, in some patients, lead to elevated titers of proinflammatory cytokines in serum. For effects on growth, the duration of exposure to these proinflammatory cytokines is important. The inflammatory cytokines interleukin 1β (Il1β), interleukin 6 (Il6) and tumor necrosis factor α (TNFα) may inhibit growth either directly at the physis or indirectly by reducing IGF-1 [43].

In addition, malnutrition in children with chronic diseases also plays an important role in growth impairment and, typically, circulating IGF-1 and GHBP levels are decreased [43, 44].

Metabolic acidosis in children with chronic renal failure (CRF) down-regulates cartilage matrix proteoglycans, collagen type 2 syntheses and expression of IGF-1 and IGF-1R in the physis, thereby, inducing GH resistance. Acidosis also changes the pulse amplitude of GH secretion, sup-presses serum IGF-1 and decreases the expression of hepatic IGF-1 mRNA, hepatic growth hormone receptor (GHR) mRNA and epiphyseal IGF-1 mRNA [44-46].

There are few reports on the abnormalities of the physis in children with CRF. One case report [47] described an 8-year old girl who died of long-standing uraemia where an absent columnar cartilage and an irregular zone of calcification were found in the physis. Several authors claim that the columnar cartilage of the physis is irregularly formed in children with CRF [43-45, 47, 48], resembling the abnormalities of the physis that are observed in SCFE [3-7].
The development of renal osteodystrophy (ROD) is one of the most severe clinical problems complicating CRF. ROD represents a range of disorders, ranging from high-turnover bone disease as a result of hyperparathyroidism to low-turnover osteomalacia and adynamic bone. Secondary hyperparathyroidism may cause growth failure by modulating genes involved in enchondral bone formation and alternating the architecture of the physis [15, 44, 49].
The risk of SCFE and/or avascular necrosis in children with CRF as a result of rhGH treatment and ROD remains equivocal. However, it is advisable to obtain radiographs of the osseous structures before GH therapy in children with CRF and growth retardation has commenced [49].
In conclusion, chronic diseases in children cause growth impairment via different mechanisms acting on the GH-IGF-1 axis. Mainly in children with CRF, where ROD can become a severe complication, physis abnormalities can look like the same abnormalities that are observed in SCFE.

Diagnostic endocrine measurements in SCFE

Endocrine evaluation of patients with SCFE is often inconclusive. Many studies have reported on hormonal measurements in patients with SCFE, including measurements of triiodothyronine (T3), thyroxine (T4), testosterone, 17B-oestradiol, thyroid-stimulating hormone (TSH), insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein 3 (IGFB3), growth hormone (GH), PTH, 1,25 dihydroxyvitamin D and cortisol levels. All plasma and urinary hormone levels in patients with SCFE were similar to controls. Also, pubertal development was normal and comparable to the controls [50-53].
One retrospective study, published in 1988, reported decreased T3, testosterone and GH levels [51]. Papavasiliou et al. [54] investigated seven boys and seven girls suffering with SCFE [54] and found that the levels of FSH, LH and testosterone were lower than expected. The investigators claimed a possible temporary hormonal dis-order, which may play a role in the development in SCFE. The results

of these studies have to be interpreted with care. Hormone assays have changed dramatically since 1988 and the number of patients in the second study was very small.

Burrow et al. [55] investigated whether clinical characteristics (gender, height, age and bilateral involvement) were useful as a screening test for patients with underlying endocrinopathy. They found that 8 % of 166 patients had an endocrinopathy. Only short stature (below the tenth percentile for height) had a high sensitivity for detecting an underlying endocrinopathy. Wells et al. [37] documented, in 7 % of 131 patients with SCFE underlying endocrinopathies, mainly hypothyroidism. Interestingly, all of the patients developed bilateral SCFE.

Jingushi et al. [56] examined the serum of 13 children with SCFE, 22 healthy children and five children with cerebral palsy. In this study, significantly lower serum levels of M-PTH (mid-portion PTH) and 1,25 di-hydroxyvitamin D was found, but this was only transient.

In conclusion, there is insufficient evidence to justify extensive hormonal screening in patients with SCFE. Temporary hormonal changes preceding SCFE have been suggested, but large prospective studies are needed in order to obtain sufficient evidence for such a hypothesis.

As a recommendation, one could test for endocrine and metabolic changes in young children (<10 years of age for girls and <12 years of age for boys) and if there is short stature below the tenth percentile for height. The most commonly affected hormones in endocrinopathies are thyroid hormones and growth hormone.

Conclusion

Slipped capital femoral epiphysis (SCFE) is the result of high load across an abnormally weak physis. Children suffering from endocrinopathies, obesity and chronic diseases have an increased risk for the development of SCFE. However, the precise pathogenesis and aetiology of SCFE is still unknown. Many endocrine factors and hormones have been described that interact on the physis in several ways. Although studies which tested blood and urine samples in children with SCFE for hormonal abnormalities were inconclusive, the transient hormonal fluctuations during puberty might be the underlying factors.

Children with overt endocrinopathies like hyper- and hypothyroidism, hyperparathyroidism, hypogonadal states and hypopituitarism seem to have a higher chance of developing SCFE. This review shows that the growth hormone–insulin-like growth factor 1 (GH-IGF-1) axis, sex hormones, leptin, thyroid hormone with Indian hedgehog– parathyroid hormone-related hormone (IHH–PTrH) feedback loop and glucocorticoids are inter-related and have direct as well as indirect effects on the human physis.

In children with chronic diseases, the use of glucocorticoids and the presence of inflammation, malnutrition and metabolic acidosis influence the extracellular matrix (ECM), the quality of the chondrocytes, as well as the activity of the GH-IGF-1 axis.

SCFE is most likely the result of a multi-factorial event during adolescence when height and weight increase dramatically and the delicate balance in the various hormonal equilibria can be disturbed. Up to now, there are no screening or diagnostic tests available to predict patients at risk for SCFE.

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CHAPTER 5

Histopathology of physes in human Slipped Capital Femoral Epiphysis

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Abstract

Introduction
Clinical features and risk factors of Slipped Capital Femoral Epiphysis (SCFE) are commonly discussed in literature, however histopathology of this disorder remains obscure. We conducted an observational study to compare histology of the physes in SCFE with normal physes to see if there was a relationship between SCFE and hormonal imbalance during puberty.

Methods
18 patients with SCFE (20 physes) and 9 controls (11 physes) were biopsied and studied histomorphologically and with immunohistochemistry, using S100 expression to highlight physes in the biopsies.

Results
The main histomorphological feature was an architectural disorder of chondrocytes in the physes of patients with SCFE. Within SCFE physes, hypertrophic chondrocytes maintained their S100 staining pattern, to comparison to these chondrocytes in control physes. Vascular proliferation was seen in only a small number of cases, suggesting that either pre- or post slippage an inflammatory response occurred. Caspase- and expression of eight hormonal receptors in chondrocytes of SCFE physes was similar to chondrocytes controls, making a role for either altered apoptosis or hormonal signalling, less likely.

Conclusion
SCFE generally shows perturbed architecture of regular aligned chondrocytes in the physis, but the phenotype of hypertrophic chondrocytes remains normal. These findings support a biomechanical cause for slippage in the hypertrophic zone. Transient hormonal imbalance, pre-slippage due to puberty, without effects on expression of receptors could not be detected but could still play a role.

Level of evidence
Observational study.

Keywords SCFE, biopsy, histomorphology, immunohistochemistry, physis, chondrocyte, cartilage

Introduction

Slipped Capital Femoral Epiphysis (SCFE) is one of the most common hip disorders in adolescence [13]. The condition is radiological characterized by displacement of the femoral neck through the physis, whilst the femoral head stays in the acetabulum. Clinical diagnosis is often based on pain in the groin or upper leg and the development of a limp. Treatment is usually through percutaneous single screw epiphysiodesis with or without gentle reposition depending on timing and stability. Prognosis is generally dependent on whether the SCFE is classified as stable or unstable and the degree of slippage on the Lauenstein radiological view [13].

The literature focuses on known risk factors and diagnostic features of SCFE but the pathogenesis of SCFE remains obscure and appears multifactorial. Little is known about the natural history of slippage of the epiphysis. Biomechanical factors, such as obesity, femoral retroversion and increased obliquity seem to play a role in SCFE[13].

SCFE occurs during puberty, so biochemical factors may also take part. In puberty, transient hormonal changes could possibly influence the physis and might be crucial in creating a weak physis of the hip that cannot resist the load-applying pressure [21]. In addition, there is an increased incidence of SCFE in children with endocrine diseases such as hypothyroidism, renal osteodystrophy, growth hormone supplements, and hypogonadal states [5, 18].

It is hypothesized that improper or dysregulated signaling, through one or more of the several hormonal pathways, leads to altered expression of hormonal receptors or its second messengers in the physes. This may result in perturbed regulation of the hypertrophic chondrocytes and altered extracellular matrix (ECM) turnover. Earlier studies of the human SCFE physis have found a marked distortion of architecture and diminished cellularity on a microscopical and ultrastructural level. Collagen fibrils were fewer and randomly oriented [2, 3, 9, 11]. Another feature was an increased frequency and distribution of chondrocytes undergoing apoptosis, which resulted in diminished numbers of chondrocytes in the human SCFE physis [1]. Evidently, the perturbed orientation of chondrocytes and the diminished collagen observed are not necessarily causal related to development of a slip and given the insidious nature of slippage, this may also represent an effect of slippage. In general, little is known about the histomorphological changes in SCFE in humans. In this study we compared chondrocytes in physes of 27 children with SCFE to

physes of controls (i.e children with normal physes) with special emphasis on their histomorphology. We registered signs of abnormality in architecture, cellular composition and vascularity in affected physes. Hormone receptors, which are known to play an important role in puberty, were stained to detect their presence or absence in the chondrocytes in the biopsies of the physes in SCFE and controls. We assessed whether slipped physes were associated with altered hormone receptor expression, showed altered vascularity or signs of increased apoptosis. The correlation with gender, age and BMI was also analyzed.

Materials and Methods

Case control design

We recruited cases and controls on the basis of hospital admission after approval of the local medical ethical committee and with informed consent of the parents/carers. Twenty biopsies of 18 patients with SCFE (2 bilateral) were taken during percutaneous epiphysiodesis. We began by performing a screw epiphysiodesis and, after securing the femoral head, the biopsy was taken using fluoroscopy through the same percutaneous incision next to the screw. All biopsies were collected with a Jamshidi needle across the physis. (8ga.X 6in, Bone Marrow Biopsy Needle, ARGON). Nine patients (11 physes) served as controls. We used specimens taken from growth plates from the foot in patients with either an amputation (Syme, below knee for tibia aplasia, 6th toe), or obtained during a percutaneous epiphysiodesis procedure for leg length difference of the proximal tibia and/or distal femur.

Clinical parameters were defined by body mass indices (BMI in kg/cm^2), defined normal when <25 and obese when ≥25 respectively, by age defined as young <11 versus adolescents ≥11 years old and by sex.

The hormone receptors, that were studied immunohistochemically were, Insulin like Growth Factor Receptor (IGHR), Growth Hormone Receptor (GHR), Estrogen Receptor α and β (ERαβ), Thyroid Receptor α and β (TRαβ), Androgen Receptor (AR) and Leptin Receptor (LR). Caspase expression served as marker for apoptosis. S100 expression was utilized for representativeness of the physes. Expression of CD34 was used as identification for endothelial cells as proxy for signs of inflammation chronicity.

Specimens and histomorphology

The biopsy specimens were fixed in 4% buffered formaldehyde, pH 7.5 and embedded in paraffin immediately after collection. Deparaffinized sections were routinely stained with H&E.

Immunohistochemistry.

Immunohistochemical analyses were performed on three µm thick sections from paraffin-embedded biopsies either routinely with the immunostainer of Roche Ventana Benchmark Ultra (Tucson, USA) or applied manually. In the latter case, the sections were deparaffinized with xylene and hydrated through grades of ethanol. Endogenous peroxidase was blocked with 0,3% H_2O_2/methanol and followed by antigen retrieval with 10 mM Tris 0,1mM EDTA pH9 (TEpH9) in a microwave for 10 minutes or with Citrate pH6 (Citr.pH6) for 20 minutes at 100°C. Tissue sections from thyroid, placenta, ovary, tonsil and stomach were used as positive controls, as well as Tissue Micro Arrays for androgen receptor (AR), Cytokeratin (Cam5.2), estrogen receptor (ER) and S100.

Details concerning the use and detection method of the antibodies are described in table 1.

Detection of the antibodies in the Benchmark Ultra the Optiview detectionkit including DAB was used in combination with CC1 at 100°C as antigen retrieval. Manual application detection was used with either the highly sensitive PowerVision Plus method (PV plus; Immunologic, Duiven, The Netherlands) for antibodies raised in mice or Envision anti-Mouse/Rabbit HRPTM (Dako, Glostrup, Denmark) for antibodies raised in rabbits. Visualization of the manual method Liquid DAB+ (Dako, Glostrup, Denmark) as chromogen was used and counterstained with Mayer's hematoxylin, dehydrated with grades of ethanol, cleared with xylene. All sections were mounted with Tissue Tek ® coverslipping film (Sakura Finetek Europe B.V., Alphen aan den Rijn, The Netherlands). (see table 1)

Immunohistochemistry was scored semiquantitively, using three categories: 'negative'(0),'slightly positive'(0.5) and'positive'(1). Staining patterns in chondrocytes were categorized in the nuclei and cytoplasm while simultaneously, the surrounding stromal cells in the metaphysis (in particular osteocytes) were assessed as controls in the same biopsy with similar subdivision in nuclear- and cytoplasmic patterns. All but one immunohistochemical procedures were duplicated. All biopsies were scored twice by two observers (MW and FvK).

Table 1
Use and detection method of the antibodies

Protein	Antibody Species/ Clone/polyclonal	Dilution	Company	Antigen retrieval	Detection
1 AR	Rabbit clone SPT107	1/50	Cellmarque Rocklin, USA	CC1	Optiview
3 Cam5.2	Mouse clone Cam5.2	1/100	BDbiosciences San Jose, USA	CC1	Optiview
4 Cleaved Caspase 3	Rabbit Polyclonal	1/100	Cell signaling technology Beverly, USA	CC1	Optiview
5 CD34	Mouse Clone QBEN10	1/50	Dako Glosstrup, Denmark	CC1	Optiview
6 ER- alpha	Rabbit SP1	1/50	Spring Bioscience Pleasanton, USA	CC1	Optiview
7 ER-beta1	Mouse clone PGG5/10	1/50 1hr	Dako Glosstrup, Denmark	Citr.pH6	PV plus
8 GH receptor	Mouse clone MAB263	1/100 16 hr	Abserotec Oxford, UK	TEpH9	PV plus
9 IGF-1R beta	Rabbit Polyclonal	1/100 16hr	Santa Cruz Dallas, USA	Citr.pH6	Envision
10 Ob-R (leptin receptor)	Mouse clone B-3	1/50 1hr	Santa Cruz Dallas, USA	TEpH9	PV plus
11 S100	Rabbit Polyclonal	1/5.000	Dako, Glosstrup, Denmark	CC1	Optiview
12 TR-alpha	Mouse clone H2804	1/2.000 1hr	Perseus proteomics R&D Tokyo, Japan	TEpH9	PV plus
13 TR-beta	Mouse clone J51	1/50 1hr	Santa Cruz Dallas, USA	TEpH9	PV plus

Statistical analysis

To determine whether the proportion of immunohistochemistry categories differed between the biopsies of the patients with SCFE and the controls, a Chi-Square test of goodness-of fit was performed. To ensure robust analyses, the likelihood ratio test statistic was used with expected values in the cell of the cross tables of less than 5. As several tests were being performed within the same sample, we treated $p \leq 0.01$ as being statistically significant.

Results

Twenty biopsies with SCFE in 18 patients and 11 control biopsies in 9 patients were taken in two university hospitals. In the children with SCFE, 12 boys (one bilateral affected) and 6 girls (one bilateral) had a mean age of 13.5 (10-15) and 11.6 (11-13) respectively at the time of surgery. Hip slips, measured from the Lauenstein radiological view, were classified as 10 mild (angle < 30 degrees), 4 moderate (30 to 50 degrees) and 6 severe (> 50 degrees). Of the slipped hips, 10 had a chronic SCFE,

4 had an acute on chronic slip, 1 had an acute slip and 3 had a pre-slip. There was no record for 2 of the hips. The slip was classified as stable in 15 hips, unstable in 1 hip and in 4 hips there was no record of weight bearing. The mean BMI in patients with SCFE was 23.4 (18.7-31.5) n=13.
Five boys and 4 girls served as controls. In one boy and one girl, a biopsy was taken of the proximal tibia and distal femur in the same procedure. The mean age in boys was 8 (1-14) and 9.8 (4-12) in girls. The BMI in the controls was 16.1 (9.9-19.2) n=8. (See table 2)

Table 2
Patients clinical features
NA=not applicable

	Case	control
Total (biopsies)	20	11
Total Pt	18	9
M v F	12 v 6	5 v 4
Age <11 v ≥11 (biopsies)	2 v 18	4 v 7
BMI <25 v ≥25 (biopsies)	9 v 4	10 v 0
Pre v acute v ac-on-chronic v chronic v unknown	3 v 1 v 4 v 10 v 2	NA
Weightbare yes v no v unknown	15 v 1 v 4	NA
Southwick angle slip mild moderate severe*	10 v 4 v 6	NA

*Mild slip <30, moderate slip 30-50, severe slip >60 degrees

Histomorphology

Biopsies differed in their physis integrity, as some biopsies showed only one site adjacent to the physis (the metaphysis). In some biopsies, physis had disappeared in the last sections due to limited material (see table 3). The main feature of the slipped physis, as seen in the biopsies taken, was a disturbed architecture of hypertrophic chondrocytes. Cells were distributed fragmentarily and haphazardly and were sometimes difficult to characterize. In general, however, they maintained their characteristic hypertrophic appearance (See figure 1A and B).
All biopsies demonstrated S100 expression in the cytoplasm of the hypertrophic chondrocytes and in all biopsies, expression was brisk. No significant differences, pertaining to S100 expression, were found between SCFE patients and the controls, nor were there significant differences between age, weight, BMI or gender (See figure 2A en 1B).

Figure 1A control HE (obj. 5x)

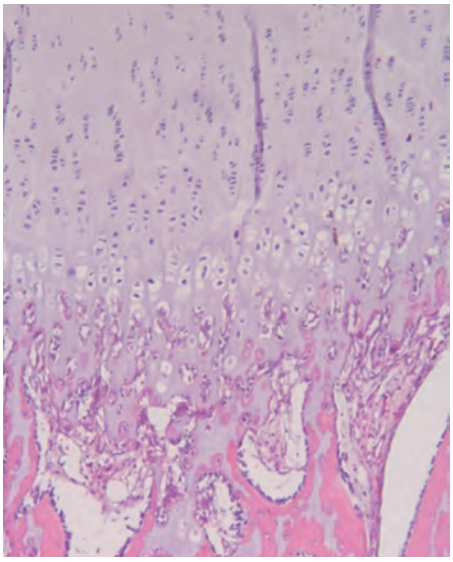


Figure 1B SCFE HE (obj 5x)

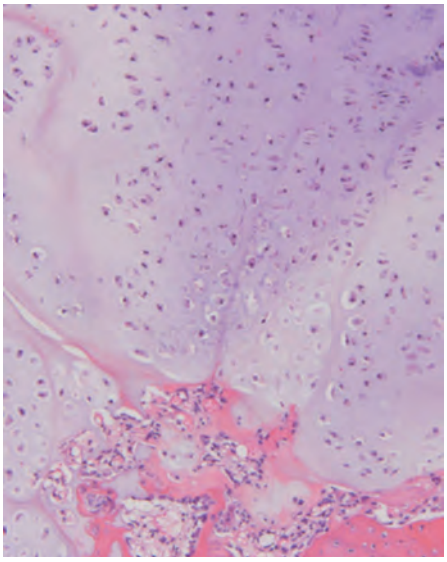


Figure 2A Control S100 staining (obj. 5x)

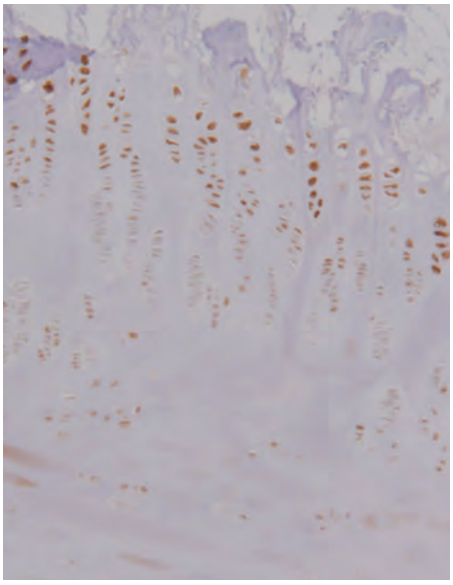
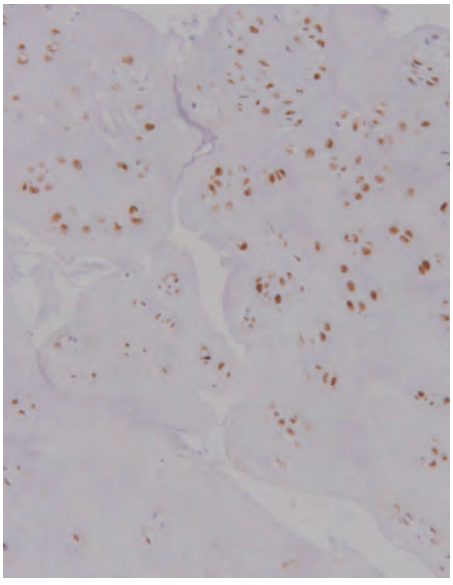


Figure 2B SCFE S100 staining (obj. 5x)



Immunohistochemistry

CD34 and Caspase activity

SCFE and controls CD34 staining was observed in the transition zone of the physis towards the metaphysis, while no signs of neovessels were seen around hypertrophic chondrocytes. In 9 SCFE cases, we did not observe signs of (increased) vascularity, while in 9 SCFE cases limited signs of increased vessels size and number were seen. For the control group there was positive vessel staining in 3 out of 10 biopsies (See figure 3A and B). No statistical differences between SCFE and the controls were noted. The expression of Caspase-3 was consistently faint to absent in all cases and controls (not shown).

Figure 3A Control CD34 staining (obj. 5x)

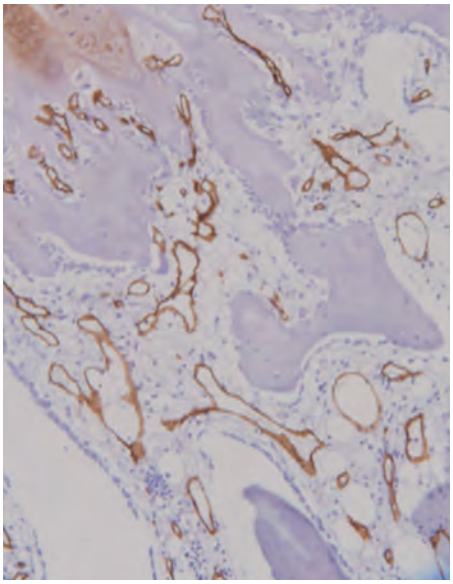
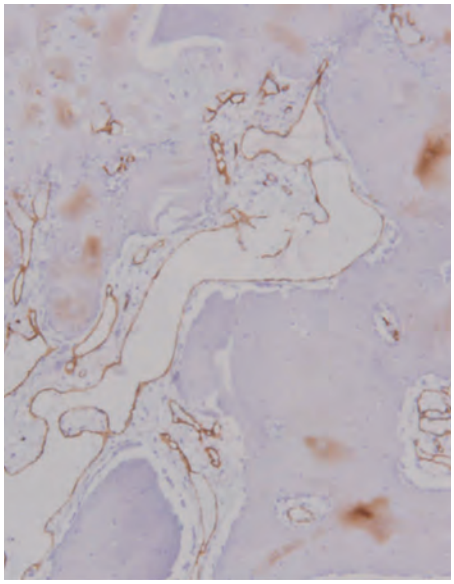


Figure 3B SCFE CD34 staining (obj. 5x)



Hormonal receptors

Expression of Insulin-like growth factor receptor (IGFR1) and growth hormone receptor expression was observed in the cytoplasm of chondrocytes and osteocytes, but showed no statistically significance between cases and controls (see figure 4A and B). Estrogen β (ER-β) receptor stained only the nucleus of both the osteocyte and chondrocyte, but showed no statistically significance between cases and controls. Thyroid receptor α was faintly expressed in cytoplasm and nucleus of the chondrocyte and osteocyte, in contrast with Thyroid receptor β, which was consistently not detected. Androgen receptor, leptin receptor and estrogen

receptor alpha (SP1) showed no expression in either SCFE cases or controls. All of the receptors did not show any statistical differences in both groups, SCFE and the controls (See table 3). We also correlated the differences in age (< or ≥11 years old), differences in sex or BMI (< or ≥ 25 kg/m2) with staining of the biopsies but found no significant relationships (data not shown). The groups acute, acute on chronic or chronic as well as stable/ unstable SCFE were too small for meaningful comparison.

Figure 4A control IGFR1 staining (obj. 5x)

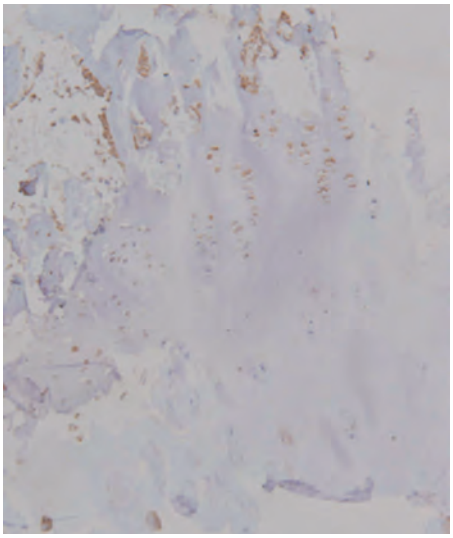
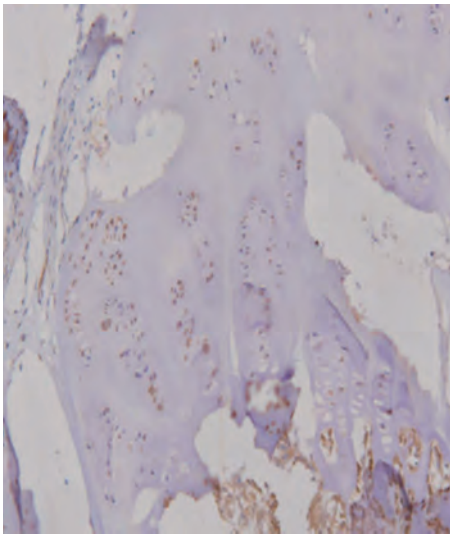


Figure 4B SCFE IGFR1 staining (obj. 5x)



Discussion

The cause and pathogenesis of SCFE remains obscure. We have studied the histomorphology of slipped physes in symptomatic patients and compared them to control physes.

The most obvious histological difference in SCFE compared with controls was consistent perturbation of the linear architecture of hypertrophic chondrocytes, a finding similar to that of other studies [2, 3, 9, 11]. The loss of longitudinal orientation of the chondrocytes in SCFE physes was probably due to tangential forces during slippage in SCFE [7]. Our findings of irregular columns are largely in line with earlier reports in the literature, as shown in table 4, but we could not confirm diminished numbers of chondrocyte [2, 10, 11, 15]. The resting zone of the epiphyses with SCFE was located outside the slipping zone and appeared to be relatively normal [2, 10, 15].

Table 3
Semiquantitative immunohistochemistry profiles of chondrocytes and bone components (osteoblasts, -clasts and - cytes) in cases and controls.

CC chondrocyte cytoplasm, CN chondrocyte nucleus, OC osteocyte cytoplasm, ON osteocyte nucleus
GHR Growth hormone receptor, TR α and β Thyroid receptor α and β, IGF insuline like growthfactor receptor

		Control				Case				
		CC	CN	OC	ON	CC	CN	OC	ON	max TOTAL
GHR	0,5			4				1		18
	1,0			5				8		
TRα	0,0	3	1	3	3	8	15	7	16	20
	0,5	0	2	0	0	9	2	17	1	
Caspase	0,0	2	1	1	1	13	13	13	9	20
	0,5	1	2	1	2	4	4	3	7	
	1,0			1				0		
Androgen R	0,0		3		3		16		16	20
	0,5		0		0		1		1	
Leptin R	0,0			1				5		19
	0,5			2				11		
Estrogen R β	0,0		3		3		8		7	20
	0,5		0		0		5		9	
	1,0		0		0		4		1	
IGF	0,0	2		0		1		1		24
	0,5	3		4		15		6		
	1,0	1		3		1		10		
S100	0,0	0				1				30
	0,5	4				2				
	1,0	6				17				
TRβ	0,0				5				18	25
	0,5				0				2	

We observed consistent staining of S100 protein in hypertrophic chondrocytes in SCFE, facilitating recognition and actually underscoring the representativeness of the biopsies [20]. Neither did we observe a difference in Caspase 3 expression between SCFE cases and controls physes, suggesting that no increased apoptosis in SCFE had occurred. Our finding did not concur with a study measuring apoptosis in hypertrophic chondrocytes in core biopsies in a patient with SCFE using the Tunel procedure [1]. It seems therefore that this phenomenon may not be representative for all cases of SCFE, since Caspase 3 is more sensitive for detecting apoptosis than the Tunel procedure [8]. Increased expression of CD34 in SCFE physes, as marker for vessel density, would point inflammatory activity accompanying slippage.

We observed increased expression in 9 out of 18 cases, making a preslippage (inflammatory) process, if it occurs, not a prerequisite for SCFE. Moreover, CD34 expression was also observed 3 of the 10 control biopsies.

Expressions of eight hormone receptors were comparable in SCFE and control cases. Since SCFE occurs during periods of altered hormone homeostasis (during puberty or in children with endocrine disease), our finding observation either suggests perturbation in signaling without altered expression (not excluding alterations in intracellular events) or a limiting role for these signals in SCFE. In our study, we observed ER-β receptor expression in osteocyte and chondrocyte nuclei, but we did not see a difference between SCFE cases and controls. In addition, we could not detect expression of either ER-α or AR in either group despite another study that reported expression in human physis [16]. Differences between our study and abovementioned study may be related to tissue specific differences in antibody (ER-6F11 vs SP1 clone) [6]. Leptin may have a direct effect on the physis through LR by increasing the width of the proliferative zone in a dose-dependent manner [21] but in our series LR expression was were very low and showed no difference in either SCFE cases or controls. A similar pattern was observed for and TR α, while TR- β receptor was not detected in either group. The expression of insulin like growth factor receptor (IGFR1) and growth hormone receptor expression was clearly observed (in cytoplasm of chondrocytes and osteocytes) but, again, showed no difference between SCFE and controls. Both growth hormone (GH) and insulin-like growth factor (IGF1) axes are reportedly active in physis growth regulation [12, 19], but we did not observe altered expression of either receptor, making a crucial role for the hormones less likely as is stated in the literature [4, 14].

Our small series has limitations. It is a crosssectional, observational study with limitations for procuring age-sex matched biopsies from normal physes or taking biopsies from controlateral sides in patients [17]. So, we cannot exclude the possibility that more proper controls, i.e. from children in a similar phase of puberty and similar physes sites, may have showed different pattern from our current controls. In other words, our lack of differential patterns of hormonal receptors does not rule out that the slip may be due to a transient imbalance of hormonal changes during puberty. In second limitation of our study may have been the timing of the biopsies: we could only take biopsies during the fixation of the femoral head which was usually 3 to 6 months or even longer after the initial slippage, giving a more restricted picture of the actual event of slippage. Finally, although the SCFE-

and control physes looked similar with the markers in this study, the molecular composition of either matrix or within cells may have been very different.

Table 4
Morphological findings in growth plates accompanying SCFE, literature review

article	N=	Resting zone N=normal A=abnormal	Disorientation columnar structure D: in hypertrophic and proliferative zone: W: widened hypertrophic zone.	Intracellular abnormalities N=normal A+abnormal;	Extracellular matrix N=normal A=abnormal
1977[17]	3 (1)	N	D (W)	N	A
1985[2, 3]	23	N	D (W)		A
1989[12]	6	N/A	D	A	A
2003[11]	18	N	D		
2005[1]	3		D		N
2009[21]	9		D		A
2010[10]	6		D	A	

First 5 Studies also mentioned presence of repair tissue and affirmed presence of slip in the hypertrophic zone.

Conclusion

SCFE generally shows a perturbed architecture of the regular aligned structures in the physis but the normal phenotype of hypertrophic chondrocytes prevail. Neither alteration in apoptosis nor in vessel density could be found, and no differences were observed in hormonal receptor expression of eight hormonal receptors which are important in puberty.

Based on our study, biomechanical seem more likely than biochemical factors as a cause of SCFE.

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CHAPTER 6

Current practice in the management of acute/unstable slipped capital femoral epiphyses in the United Kingdom and the Netherlands: results of a survey of the membership of the British Society of Children's Orthopaedic Surgery and the Werkgroep Kinder Orthopaedie.

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J Pediatr Orthop B. 2007 Mar;16(2):79-83.

Abstract

A questionnaire was sent to all members of the British Society for Children's Orthopaedic Surgery and the Werkgroep Kinder Orthopaedie to identify points of agreement/disagreement on the management of the acute unstable slip of the upper femoral epiphysis and to compare these European results with those from a similar North American survey. Sixty-five per cent responded. Overall, both countries evaluated cases similarly and believed in their urgent management.
Sixty-six per cent did not reposition the slip. Significant differences were observed in attitude towards single screw usage, prophylactic pinning and metalwork removal both between the two countries and in comparison with North America.

Keywords: acute, survey results, unstable slipped capital femoral epiphysis

Introduction

Slipped capital femoral epiphysis (SCFE) has been classified traditionally into preslip, acute, acute-on-chronic and chronic phases [1]. A more recent classification, stable and unstable, relates to weight-bearing ability and is considered more prognostic [2].

The incidence of SCFE is between 0.2 and 10 per 100 000 and 10–15% of cases of SCFE are considered to be acute and/or unstable [1]. The clinical criterion for a diagnosis of an acute SCFE is symptoms for duration of fewer than 3 weeks, although, in the views of many people, the true acute SCFE will have an unstable epiphysis that may be visible on dynamic screening or at open reduction.

The literature is controversial regarding the management of an acute, unstable SCFE. The two most severe complications of an unstable SCFE are avascular necrosis (AVN) and chondrolysis and the first aim of treatment is to avoid these complications if possible.

Tokmakova [3] reviewed a group of 240 patients with SCFE. Twenty-one patients developed AVN and all were unstable SCFE. Other factors that were correlated with AVN were degree of slip, the number of pins used and whether there was partial or complete reduction of the slip.

One of the major questions is whether repositioning of the epiphysis is advisable or not. De Sanctis [4] and Arnold [5] contradict Tokmakova [3]. They claim that preoperative reduction with very gentle manipulation and percutaneous fixation with a single screw [4] and K-wires [5], respectively, is the best treatment for acute SCFE and reduces the risk of AVN and chondrolysis.

Recently, a questionnaire was sent to all Pediatric Orthopaedic Society of North America members to survey their ideas on management [6]. Only 33.1% (263 of 794) responded. An agreement was reached on the method of patient evaluation, but discrepancies remained in the use of classification systems and fixation methods.

We used a similar questionnaire and our goal was to compare two European countries with each other and with the POSNA survey and to audit our treatment of acute/unstable SCFE.

Methods

The Evidence Analysis Work Group of the Pediatric Orthopaedic Society of North America devised a survey to obtain basic demographic and volume data on the members of the society managing acute unstable SCFE [6]. The survey also aimed to address areas of controversy in the management of this condition. Our questionnaire was based on the same elements and was distributed to orthopaedic surgeons in both the United Kingdom (UK) and the Netherlands with an expressed interest and expertise in paediatric orthopaedics. These surgeons were identified by their membership of either the British Society of Children's Orthopaedic Surgery or the Werkgroep Kinder Orthopaedie. Initial contact was by e-mail when such an address was available, otherwise a work fax number was used. The use of free text comments was encouraged. All nonrespondents were sent a reminder: in the UK, by fax and in the Netherlands, by post. We excluded clinicians who were retired or who explicitly stated that their practice did not include urgent/emergency work such as this. We also excluded overseas members of both societies.

Statistical analysis

All responses were collected and data entered initially into an Excel spreadsheet (Microsoft, Redmond, Washington, USA). The data were subsequently transferred to a SPSS file for statistical analysis. The results for the UK and for the Netherlands were compared with each other (and with the results from the POSNA survey) using the Pearson χ^2 test and SPSS version 12.0 software (SPSS Inc., Chicago, Illinois, USA). A *P* value of less than 0.05 was taken to be significant.

Results

A total of 220 questionnaires were distributed (149 in the UK and 71 in the Netherlands). The overall response rate was 65% (142 surgeons) and was similar for both countries. A complete review of all responses from both societies is presented in Table 1.

Among respondents, the median duration of consultant practice was 11 years (mean 12.9, range 1–35 years). Overall, 63% of these surgeons spend more than half their time in paediatric orthopaedic practice.

Table 1.
Summary of the results of the questionnaire distributed to members of the British Society of Children's Orthopaedic Surgery (BSCOS) and Werkgroep Kinder Orthopaedie (WKO) with a comparison with the POSNA study [6]

	BSCOS	WKO		POSNA
	United Kingdom (n = 149)	Netherlands (n = 71)	Total (n = 220)	n = 794
Number of respondents (% of society members)	99 (65)	43 (65)	142 (65)	263 (33)
Median (range) of years in practice	12.6 (1–35)	13.9 (1–30)	12.9 (1–35)	15 (1–42)
Paid workload (n = 135)*				
75–100	29%	51%	36%	
50–75	37%	5%	27%	
25–50	28%	18%	25%	
0–25	6%	26%	12%	
Classification (n = 133)*				
Acute/chronic	8%	35%	16%	27%
Unstable/stable	17%	14%	16%	73%
Both	75%	51%	68%	0%
Evaluation (n = 135)				
Plain radiographs: two views	100%	100%	100%	97%
Dynamic screening	8%	3%	7%	
Magnetic resonance imaging	15%	13%	14%	1%
Computed tomography	10%	8%	10%	
Bone scan	7%	5%	7%	2%
Other	3%	0%	2%	
Combination	34%	25%	30%	
Treatment timing (n = 134)				
< 6 h	18%	23%	19%	31%
< 24 h	72%	62%	69%	57%
< 48 h	9%	13%	10%	
> 48 h	1%	2%	2%	12%
Patient positioning (n = 134)*				
Traction table	78%	46%	69%	66%
Free on radiolucent table	19%	54%	29%	33%
Other	3%		2%	2%
Treatment method (n = 136)				
Open fixation	11%	18%	13%	3%
Percutaneous fixation	89%	87%	88%	96%
Variable	12%	5%	9%	
Reposition of head (n = 131)				
Yes	29%	41%	32%	12%
No	69%	59%	66%	
Both	2%	0%	2%	
Treatment fixation (n = 136)				
Single screw	84%	69%	79%	57%
Two screws	12%	31%	18%	40%

Table 1.
Continued

	BSCOS	WKO		POSNA
	United Kingdom (*n* = 149)	Netherlands (*n* = 71)	Total (*n* = 220)	*n* = 794
K-wires	3%	3%	3%	
Variable	2%	0%	1%	
Capsular compression (n = 133)				
Yes–open	4%	13%	6%	10%
Yes–by aspiration	28%	10%	23%	26%
No	68%	77%	71%	65%
Prophylactic pinning (*n* = 135)*				
Yes	6%	15%	9%	12%
No	9%	36%	17%	88%
Depends	85%	49%	74%	
Removal of metalwork (n = 135)*				
Yes	17%	33%	21%	12%
No	34%	39%	36%	88%
Depends	49%	28%	43%	

Assessment

All surgeons used plain radiographs in two planes (antero-posterior and frog-lateral pelvic views) for their preoperative assessment but additional imaging was used by 30% of both groups. This imaging included computed tomography, magnetic resonance imaging and bone scans. Dynamic fluoroscopy was also mentioned by some to aid the assessment of stability as was the use of ultrasound and the Billings lateral radiograph. Bone age radiographs were used as an aid to planning management of the slipped and the normal sides by 6.7% with similar use in both countries.

The survey showed that, overall, 68% of respondents used both the acute/chronic and the unstable/stable methods of classification. Some significant differences were observed within the subgroups of this study. The use of both systems was more common in those with a larger paediatric practice (> 50% of workload) than in those with a more mixed practice, 74% compared with 58% ($P < 0.05$); and in the UK rather than in the Netherlands, 75% compared with 51% ($P < 0.05$). The Southwick classification [7] was used by only eight surgeons (5%).

Treatment

Eighty-eight per cent of respondents treated the acute/unstable SCFE within 24 h of presentation. Some applied skin traction on admission and before surgery. Overall, a traction table was used by 69% of surgeons but there was a significant difference between the two countries, with 78% of British surgeons using the table compared with 46% of the Dutch ($P < 0.05$).

Sixty-six per cent of surgeons did not reposition the slip. If repositioning was performed, it was done gently or it occurred as an 'accidental' repositioning as the patient was placed on the traction table for an 'in-situ' fixation. Overall, 23% would aspirate the joint as part of the perioperative assessment. This approach was more than twice as common in the UK as it was in the Netherlands. Haemarthrosis suggested that there was an acute slip present and in such instances a gentle reposition was performed. A formal decompression of the joint was only performed by 29% of surgeons – the remaining 71% never decompressed the joint.

Many surgeons highlighted the fact that a reduction of the acute, unstable SCFE should only be considered within the first 24 h of presentation. Patients presenting later would need to wait before an 'urgent' elective procedure such as a cuneiform osteotomy [8,9] could be performed. The recommended delay varied from 5 days to 3 weeks.

Percutaneous screw fixation was performed by 88% of the group with many surgeons commenting that this method was only used within 24 h of the acute event rather than within 24 h of presentation to the hospital. Treatment also varied with years of experience. Percutaneous fixation was more common (93%) in those surgeons with less than 15 years of experience. Those with more than 15 years experience opted for an open reduction and internal fixation in 21% of cases. This difference in attitude to management with increasing experience was statistically significant ($P < 0.05$).

A single screw was the most common fixation method (79%). In the group with > 15 years experience, 30% opted for two screws versus 14% in the group with < 15 years experience ($P < 0.05$). Some of the more senior surgeons felt that rotational stability was enhanced by the use of two screws.

Seventy-four per cent of surgeons admitted that the decision of whether or not to offer prophylactic pinning of the contralateral normal side depended on a variety of different factors that could vary from patient to patient. The factors quoted included co-morbidities such as obesity, endocrinological disorders, syndromes such as trisomy 21, and perhaps most importantly, the under-standing of the

family regarding the development of new symptoms from the normal hip. Among surgeons in the UK, 6% always offered prophylactic pinning of the normal side and 9% never did. These results were significantly different from those in the Dutch group in which 15% always and 36% never pinned the normal hip ($P<0.05$).
Eighty-two per cent of surgeons with less than 15 years of experience will pin prophylactically in certain circumstances compared with 53% of the group with more than 15 years experience ($P<0.001$).
Overall, 21% of respondents always remove the metal work after fusion of the physis, but 43% felt that the decision to remove the metal would depend on factors such as a complaint of pain, unsatisfactory screw position, the possibility of a second operation or signs of AVN. Again, significant differences were found between the Dutch and the British: the British surgeons were less likely to remove metalwork than their Dutch colleagues ($P < 0.05$). In both countries, however, the more experienced surgeons were less likely to remove the metalwork. Surgeons who advised removal of metalwork tended to leave the screws protruding from the lateral femoral cortex to aid the removal process.

Discussion

The treatment of an acute, unstable SCFE remains controversial. In this study, there was general agreement on the method of evaluation of such a case both within each country and between the two countries and this also agreed with the results of the POSNA study [6].
As in North America, plain radiographs are used universally for the assessment of an acute unstable SCFE but a surprising number of surgeons (30%) used other imaging techniques as well.
The use of a traction table for patient positioning is very common in the UK and more so than in North America [6], while more than 50% of the Dutch were happier to have the patient lying free on a radiolucent table. Blasier [10] showed that operating time was prolonged significantly when a fracture table was used but with no significant difference in screw position in a group of stable SCFE. This could be different for the unstable slip. The future might involve computer-assisted cannulated screw fixation, although at the moment this is associated with high additional costs [3].

Eighty-eight per cent of our study group felt that an acute, unstable SCFE was an urgent situation and definitive management should take place within 24 h of the event. These figures are probably the same as in the POSNA study [6] in which only 12% of surgeons felt that the case could be 'added to the elective schedule'. Sixty-six per cent of respondents stated that they do not reposition the slip but it may be that in some cases the administration of a general anaesthetic and the process of positioning the patient on the operating table actually result in an improvement of the relationship between the epiphysis and the metaphysis. The free text sections of the questionnaire provoked considerable comment regarding the concept of 'gentle repositioning'. From the literature, there appears to be a 'cut-off' point around 24 hours [11–13] after which the incidence of AVN is likely to rise. In the study by Peterson [11], if manipulation and fixation occurred within 24 hours of presentation, the AVN rate was 7% but this increased to 20% if similar management occurred after 24 hours. The major source of blood supply to the epiphysis is through the posterior–superior retinacular vessels. Bone scans on admission demonstrate the relationship between instability of the physis and abnormal blood supply to the head suggesting that the most likely cause of AVN lies in the initial displacement caused by the injury [14,15] An increasing suggestion is found in the literature that decompression of the hip joint by aspiration [16] or with a more formal arthrotomy [17,18] reduces the rate of AVN following displaced femoral neck fractures in the paediatric population. No published evidence supports this approach in the management of the acute, unstable SCFE and yet 29% of surgeons in this study do decompress the joint. A similar extrapolation of principles was noted in the POSNA study in which 36% of respondents decompress the capsule.

In keeping with the literature, which demonstrates a tendency to operate percutaneously and use one screw fixation [3,4,12,19–24], most of our respondents (79%) used a single screw. Interestingly, the use of a second screw was significantly higher in those surgeons with more experience. In the POSNA study [6], a greater percentage used two screws (40%) but no comment is made as to whether this was more likely to occur if the surgeon was more experienced or not.

Although Mooney et al. [6] suggest that many European centers favor prophylactic pinning of the normal side, it was only offered routinely by 6% of UK surgeons and 15% of Dutch surgeons, although more senior surgeons were more likely to perform prophylactic fixation than their junior colleagues. Thus, overall, this study

of two European centers shows a slightly lower rate (9%) of prophylactic pinning than was noted in the POSNA study (12%) [6].
Despite the known difficulties associated with the removal of metalwork in cases of SCFE, overall 21% of our study group admitted to always removing the implants. In contrast to the POSNA study [6], removal of metalwork was less likely with an experienced surgeon.
One of the limitations of this study is that we have only surveyed orthopaedic surgeons who are members of the Dutch or British Paediatric Orthopaedic Society. In both countries, orthopaedic surgeons who are not members of these societies do treat these children as well and their views may differ. Similarly, no questionnaire can cover all the factors that a surgeon considers when determining a management plan for a patient with an acute, unstable SCFE as was highlighted by the number of free text comments that were added to the questionnaire. The aim of this study was to audit the assessment and management of the acute/unstable SCFE and despite the deficiencies of the study, significant, interesting information has been obtained that highlights the similarities and differences in the management of this condition between two European countries. The comparison with the POSNA [6] study also emphasizes some perhaps unexpected similarities and differences with regard to method of fixation, prophylactic fixation and removal of metalwork. Such surveys remind us that cultural influences may affect our attitudes to management perhaps by differences in the understanding and interpretation of scientific data. The design of any multicentre study hoping to identify the most effective method of management may need to take this into consideration.

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CHAPTER 7

The results of downgrading moderate and severe slipped capital femoral epiphysis by an early Imhauser femur osteotomy

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Abstract

Purpose

Patients with moderate and severe slipped capital femoral epiphysis (SCFE) develop osteoarthritis earlier in life in association with mechanical impingement.

Methods

To correct deformity and diminish impingement, we performed epiphysiodesis combined with an Imhauser intertrochanteric osteotomy (ITO) in moderate and severe slipped capital femoral epiphysis. We downgraded the angle of the head relative to the acetabulum into an angle corresponding to a mild slip or even an anatomical position. Our hypothesis is that the avoidance of anterior impingement at an early stage can prevent the development of osteoarthritis.

Results

The results of 28 patients (32 hips) were evaluated. Outcome parameters were SF-36, Harris Hip Score, range of motion, Kellgren–Lawrence score, chondrolysis and avascular necrosis. After a median follow-up of 8 (range 2–25) years, the group was clinically, functionally and socially performing well. Radiologically, there was no sign of chondrolysis or avascular necrosis, and more than 80% of the patients did not show any signs of osteoarthritis.

Conclusions

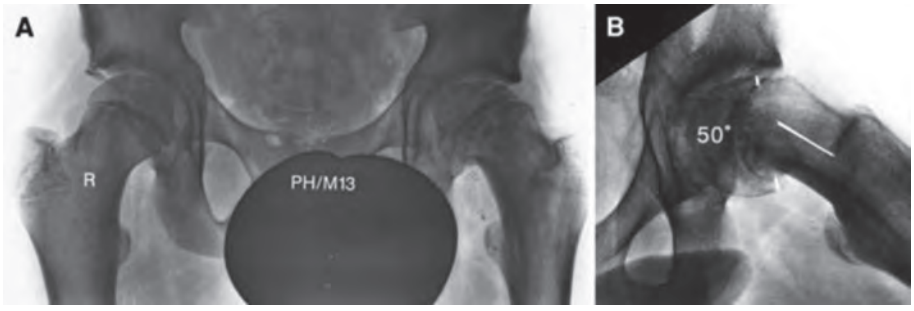
Based on these results, we conclude that a one-stage Imhauser ITO combined with epiphysiodesis performed on patients with moderate and severe SFCE gives satisfactory results.

Keywords Epiphysiodesis, Epiphysiolysis capites femoris, Imhauser osteotomy, Intertrochanteric osteotomy, Slipped capital femoral epiphysis, Slipped upper femoral epiphysis

Introduction

The long-term prognosis of slipped capital femoral epiphysis (SCFE) is largely influenced by the residual deformity, which in turn is related to the extent of slip. One of the methods for classifying the extent of slip is the Southwick classification [1, 2] which, based on lateral head shaft angle, places slip into one of three categories: mild (<30°), moderate (30–60°) and severe (>60°). The femoral head is mostly displaced medially and posteriorly. This displacement causes the metaphysis to move upward and laterally in relation to the femoral head, possibly resulting in anterior impingement with flexion of the hip [3] (Fig. 1a, b). It is thought that repetitive early mechanical abrasion of the prominent metaphysis against the anterior rim of the acetabular cartilage can trigger osteoarthritis [4, 5]. Patients with mild SCFE (<30°) have good prognoses, but patients with moderate and severe SCFE have an increased chance of developing osteoarthritis [6-8].

Fig. 1.
Pre-operative slipped capital femoral epiphysis (SCFE)



The primary objective of SCFE treatments is stopping further slippage, chondrolysis and avascular necrosis (AVN). The choice of treatment is also influenced by the stability of the slip, as described by Loder [9]. In cases of unstable SCFE, most surgeons perform an early gentle reduction of the head followed by epiphysiodesis; for stable slips, the standard approach is to stabilize the slip by in situ epiphysiodesis without reduction [10].
Various techniques have been described to correct the residual deformity. Some authors recommend performing an intertrochanteric osteotomy (ITO) as a secondary procedure after closure of the growth plate [11, 12]. In cases of severe chronic slips, many authors advice performing a subcapital osteotomy to correct

the deformity completely; however, this procedure can have a high incidence of AVN and chondrolysis [13-18].
We hypothesized that an early ITO performed concurrently with the epiphysiodesis in patients with a moderate or severe slip of the femoral epiphysis would prevent the metaphysis from damaging the anterior part of the acetabulum and, thereby, diminish the incidence of osteoarthritis at a later stage. We also expected that the occurrence of chondrolysis and AVN would be low or absent with this procedure.
The aim of the study reported here was to investigate the outcomes of epiphysiodesis combined with an Imhauser ITO performed in one session in moderate and severe slips. The objective of this combined surgical approach is to improve the position of the head in relationship to the acetabulum in order to obtain better prognostic features.

Materials and methods

Subjects

This retrospective study assesses the results of a consecutive series of 28 patients who had moderate to severe SCFE in a total of 32 hips. These patients were treated with a combined epiphysiodesis and Imhauser ITO performed by the same surgeon at the AMC Amsterdam between 1978 and 2003. Patient data are presented in Table 1. A total of 13 patients had bilateral slips versus 15 who had unilateral slips. Of the 13 bilateral patients, four underwent bilateral ITO simultaneously. The other nine had a moderate to severe SCFE on one side only and a mild slip contralaterally and underwent only a K-wire transfixation on the controlateral side. A review of the medical histories of this patient cohort revealed that 13 patients had sustained a trauma. None of the patients had a deviant endocrinological history.
Approval of the medical ethical committee was obtained.

Surgery

Prior to surgery, patients were treated by bed rest on springs and slings for an average of 14 (range 0–28) days. During this time, we designed a time-schedule for operating on the patient. We did not perform gentle reduction on any of our patients. A cannulated screw epiphysiodesis was performed via an open procedure with the use of one 5.0-mm screw. During the same surgical session, following the epiphysiodesis, the Imhauser three-dimensional ITO was performed and fixed with a 90° blade plate [19] (Fig. 2a, b). Thus, the alignment of the head

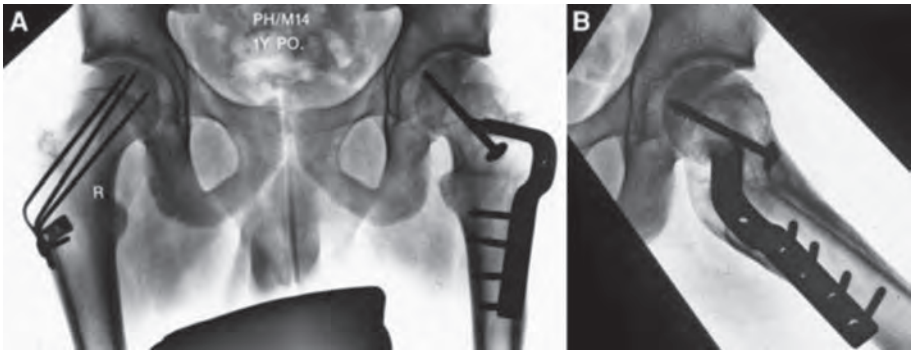
was changed in three directions relative to the acetabulum: flexion, varus and derotation. Peroperative fluoroscopy was performed to verify the position of the seating chisel and screws. All patients with an unilateral slipped hip were treated with a preventive K-wire fixation at the contralateral hip. Patients were not allowed to bear weight for 6 weeks.

Table 1.
Patient data

Demographic/clinical data	Patient cohort (n = 28)	
Gender ratio of patient cohort, *n*	M: 16, F: 12	
Mean age at surgery, years	13	(range 9–17)
Unilateral (left/right), *n*	15	(10/5)
Bilateral, *n*	13	
ITO unilateral (left/right), *n*	24	(15/9)
ITO bilateral, *n*	4	
Acute on chronic, *n*	5	
Chronic (hips), *n*	27	
Trauma in history, *n*	13	

ITO intertrochanteric osteotomy; *M* male; *F* female

Fig. 2.
One-year postoperative SCFE after epiphysiodesis and Imhauser osteotomy



Outcome assessments

Data are based on patients' notes and the X-ray results. Patients were traced and asked to complete questionnaires [part of the Harris Hip Score (HHS) and Short-Form Health Survey (SF-36)] at home; they also were invited for a clinical and radiological evaluation.

The range of motion and body mass index (BMI) were determined during the clinical examination, and hip function was measured using the HHS [20]. The completed SF-36 questionnaire was used as a measure of the general health of the patients relative to the Dutch general population [21].
Osteoarthritis of the hip at follow-up was quantified from the X-rays using the Kellgren–Lawrence scale (0–4) [22, 23]. The presence of chondrolysis and avascular necrosis was also assessed from the X-rays. Of the six patients who were not able to come to the clinic, the most recent X-rays available were used instead.

Statistical analysis

Results were analyzed using SPSS ver. 12.0 software (SPSS, Chicago, IL). Due to skewed distributions, continuous data (HHS, SF36, range of motion) were described as medians and ranges. The outcomes were analyzed non-parametrically using Mann–Whitney *U* tests in for independent comparisons and Wilcoxon signed-rank tests for pre- and post-operative comparisons. Categorical variables were described as numbers and percentages and were compared using the chi-square test. A p value <0.05 was taken to be significant.

Results

Of the 28 patients, 24 responded to the questionnaires. Twenty-two patients were able to come to the clinic for re-assessment and radiographic evaluation. The median period of follow-up of all patients was 8.2 years (range 2.0–25.7).
Two early postoperative complications were seen. The first was a leaking wound without infection, and the second was a patient who developed calf thrombosis in the operated leg. Both complications were successfully treated. No long-term complications occurred.
All osteotomies healed uneventfully. Neither chondrolysis nor avascular necrosis were seen on the X-rays.
Of the 32 slips, 22 were classified moderate and ten as severe. From the 22 moderate slips, 21 were downgraded to a mild slip and one was still a moderate slip (from 52° to 35°). Of the ten severe slips, seven were downgraded to moderate slips and three were even downgraded to mild slips. The mean slip was significantly improved from 52° (range: 30–74°) to 22° (range 0–56°) ($P < 0.01$).

Compared to the preoperative examination, the range of motion was significantly improved 1 year after the operation and also at the last clinical examination (Table 2). The HHS had an 'excellent' median score of 93 (range 49–100), with 17 (71%) patients scoring excellent/good and seven (29%) scoring fair/poor. The outcomes of the SF-36 were not significantly different from the those of the Dutch general population match for age [21] (Table 3).

The Kellgren–Lawrence score in our group was ≤1 in 80% on the anteroposterior X-ray and ≤1 in 100% on the false profile X-ray. Chondrolysis and AVN were not observed.

The preoperative lateral head shaft angle was not correlated with the outcome variables HHS, SF-36 and the Kellgren–Lawrence score. These outcome variables were also not correlated by the length of the follow-up.

Whereas normal values for BMI are between 19 and 25 kg/m^2 [24], in our group the BMI was 26.1 (range 18.7–39.1) kg/m^2 preoperatively and 28.5 (range 16.3–47.5) kg/m^2 at the last follow-up. More than half of the patients were and continued to be overweight.

Table 2.
Outcomes of the clinical examination (n = 28)

Range of motion	Time point					
	Pre-operative		1-year post-operative		Last follow-up	
Flexion (°)	97	(40–140)	113	(90–140)*	108	(70–125)*
Adduction (°)	20	(0–40)	26	(10–50)*	25	(10–40)*
Abduction (°)	33	(10–66)	39	(20–60)	41	(25–55)*
Internal rotation (°)	-12	(-45–45)	24	(0–40)*	25	(-15–50)*
External rotation (°)	53	(20–80)	50	(30–75)	46	(10–70)

All values are given as the mean, with the range given in parenthesis * $p < 0.05$ compared to pre-operative status

Discussion

We have evaluated the long-term results following the treatment of moderate and severe SCFE with an epiphysiodesis and an ITO in one session. By performing the osteotomy, we were able to downgrade the severe and moderate slips into moderate and mild slips and even, if possible, into an anatomical position to improve the position of the head relative to the acetabulum.

Table 3.
Outcome SF-36 ($n = 24$)

SF-36 measure	PF	RP	BP	GH	VT	SF	RE	MH
Study population (median)	83	100	79	80	68	100	100	86
Study population (mean ± SD), $n = 28$	76 ± 26	70 ± 42	72 ± 31	77 ± 21	68 ± 24	82 ± 29	88 ± 40	81 ± 18
Norm NL data (age 16–35 years) (mean ± SD), $n = 530$	93 ± 10.6	86 ± 28.2	82 ± 18.6	79 ± 16.8	71 ± 16.0	88 ± 18.5	84 ± 30.4	79 ± 15.0

SF-36 Short Form Health Survey; *PF* physical functioning; *RP* role physical; *BP* bodily pain; *GH* general health; *VT* vitality; *SF* social functioning; *RE* role emotional; *MH* mental health; *NL* Netherlands; *SD* standard deviation

Table 4.
Literature overview of the long-term results of corrective ITO for SCFE

Author, Year	ITO (n)	Lateral head-shaft angle (°)	Follow-up (years)	Scoring system	Excellent/good (%)	Fair/poor (%)
Parsch et al. 1999 [37]	49	40 (20–50) 7 (>50)	3	Iowa	84	6
Maussen et al. 1990 [32]	26	10: 30–40 16: 40–60	21	D'Aubigné Kellgren	77% maximum score	1 of 10 OA 15 of 16 OA
Kartenbender et al. 2000 [38]	35 (15 second stage)	51 (30–75)	23	Southwick class	77 clinical, 67 radiological	23 clinical 33 radiological
Schai et al. 1996 [30]	51	30–60	24	D'Aubigné	55	45
Carney and Weinstein [6]	29		31	Iowa Radiograph		Mean fair 2.5 (0–3)
Jerre et al. 1996 [29]	11	61.3	51.4	HHS	36	64

SCFE slipped capital femoral epiphysis; *OA* osteoarthritis

Previous cohort studies reported a relationship between the severity of the slip and the incidence of osteoarthritis. Carney and Weinstein [6] described a group of 28 patients (31 hips) with 41 years of follow-up. The 17 mild slips scored significantly better in terms of radiological grade assessment and Iowa Hip Rating than the 14 moderate and severe slips. Hansson et al. [7] claimed that mild slips can give excellent results as well; however, they stated that more long-term studies are needed to determine whether corrective osteotomies are required for slips >30°. Nordberg et al. [8] also concluded, after reviewing the long-term results of 49 patients, that patients with pronounced slipping have the highest incidence of arthrosis.

The risk of osteoarthritis is thought to be associated with repetitive trauma between the femoral metaphysis and acetabulum during flexion. It has been shown that anterior impingement by the prominent metaphysis can damage the anterior part of the acetabulum [4, 25].

Although most slips have remodeling potential, there may not be enough to prevent osteoarthritis in moderate and severe slips. In their respective patient series with severe slips, Wong-Chung and Strong [26] reported the remodeling to be only 11.7° and Bellman et al., to be only 13.5° [27]. This is not nearly enough to remodel the severe slip to a mild slip.

To prevent damage to the anterior part of the acetabulum, an osteotomy can be performed to correct the lateral head shaft angle. Both subcapital and intertrochanteric osteotomies have been described. The anatomical position can be better regained with a subcapital osteotomy; however, this procedure can be associated with high rates of AVN and chondrolysis, varying from 4.5% up to 28.5% [15, 17]. Dab et al. [28] compared the ITO with the sub-capital osteotomy and concluded that ITO is a safe, effective and reproducible realignment procedure. This conclusion supports our findings. No sign of chondrolysis and AVN was observed in any of our patients, and all osteotomies healed uneventfully. Jerri et al. [29] described a better short-term outcome of the ITO (11 patients) in comparison with the subcapital osteotomy (22 patients). However, their long-term results of the ITO were worse (see Table 4), which may have been caused by the fact that they used an older ITO technique (before the Southwick ITO was introduced).

The timing of performing the osteotomy relative to the epiphysiodesis is controversial. Performing the ITO at an early phase should be beneficial if damage by impingement plays a role in the etiology of osteoarthritis. Other options are to perform the osteotomy at closure of the growth plate or with a decline in the range of motion [5, 11, 12]. Theoretically, the less the anterior acetabulum is exposed

to abrasion from the prominent metaphysic, the better. For this reason, we advocate performing an ITO at the same time as the epiphysiodesis [30, 31]. This also eliminates the necessity of a second surgery, thereby reducing the burden for the patient. To date, we have not found indications of severe osteoarthritis based on the Kellgren–Lawrence scale. Nevertheless, Maussen et al. [32] showed in their cohort that patients with severe slips performed worse in later life, even after an intertrochanteric corrective osteotomy. In our study, we did not observe any relationship between preoperative lateral head shaft angle and the outcome parameters.

A number of studies have evaluated the outcome of the corrective ITO itself (Table 4). The use of different scoring systems of hip function and different methods of evaluating the radiographs makes it difficult to compare these studies. Unfortunately, in many previous studies, the timing of the ITO procedure relative to the epiphysiodesis was not reported. If the osteotomy is performed much later than the epiphysiodesis, damage may already have occurred to initiate a degenerative process. In general, the studies show that the outcome gets worse with the length of follow-up time. In our study, we were unable to detect a relation between follow-up time and outcome variables. However, a larger study population and a longer follow-up time may be needed to detect such a relationship.

The occurrence of SCFE is known to be related to BMI [33-35]. As expected, the BMI in our group was high, with more than half of our patients being overweight. Based on the increasing obesity problem in children in Europe and the USA, it is likely that the incidence of SCFE will increase. An increase in SCFE has already been shown in Japan [36]. Based on current knowledge, the optimal treatment of SCFE cannot yet be established. Since most effects of SCFE only become apparent after many years, more long-term studies are needed in which treatment and outcome variables are standardized.

Conclusion

Based on the results of our study, we conclude that performing an epihysiodesis at the same time as an Imhauser ITO to prevent early impingement on the anterior acetabulum in moderate and severe SFCE gives early satisfactory results. After a follow-up period of 8 (range: 2–25) years, all of our patients in the study group are performing well clinically, functionally and socially. The X-rays showed no signs of chondrolysis or AVN, and more than 80% of the patients did not show any signs of osteoarthritis.

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CHAPTER 8

Progressive slip after removal of screw fixation in slipped capital femoral epiphysis: two case reports

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J Med Case Rep. 2012 Nov 26;6:405.

Abstract

*Introduction**:***
In slipped capital femoral epiphysis the femoral neck displaces relative to the head due to weakening of the epiphysis. Early recognition and adequate surgical fixation is essential for a good functional outcome. The fixation should be secured until the closure of the epiphysis to prevent further slippage. A slipped capital femoral epiphysis should not be confused with a femoral neck fracture.

Case presentation:
Case 1 concerns a 15-year-old boy with an adequate initial screw fixation of his slipped capital femoral epiphysis. Unfortunately, it was thought that the epiphysis had healed and the screw was removed after 11 weeks. This caused new instability with a progressive slip of the femoral epiphysis and subsequently re-fixation and a subtrochanteric correction osteotomy was obligatory. Case 2 concerns a 13-year-old girl with persistent hip pain after screw fixation for slipped capital femoral epiphysis. The screw was removed as lysis was seen around the screw on the hip X-ray. This operation created a new unstable situation and the slip progressed resulting in poor hip function. A correction osteotomy with re-screw fixation was performed with a good functional result.

Conclusion:
A slipped epiphysis of the hip is not considered 'healed' after a few months. Given the risk of progression of the slip the fixation material cannot be removed before closure of the growth plate.

Introduction

Slipped capital femoral epiphysis (SCFE) is the most common adolescent hip disorder. In this condition the metaphysis of the femoral neck displaces anteriorly and superiorly to the femoral head [1]. The epiphysis weakens and eventually fails due to a combination of biomechanical and biological factors [1,2]. This is in contrast to the rare adolescent hip fractures caused by high-energy trauma [3,4]. For a good functional outcome, early recognition and adequate surgical treatment is essential in both cases. In some cases of SCFE the surgical principles of fracture treatment with hardware removal are still used which can lead to a poor outcome [2]. We present two cases with complications after screw removal to highlight the serious consequences of the loss of adequate fixation before the end of growth plate closure.

Case presentation

Patient 1

A 15-year-old obese boy visited our clinic with a painful hip on the left side. The complaints arose one year earlier after he had fallen on his hip. At that time a mild epiphysiolysis was diagnosed on presentation in the emergency room. He was admitted with bed rest and three days later an *in situ* fixation was performed with one cannulated screw (Figure 1). The postoperative recovery was without complications and he was pain free after a few weeks. As it was thought that the fracture had consolidated, the screw was removed 11 weeks after initial placement. After this procedure had been performed his hip became increasingly painful and he experienced reduced mobility. Ten weeks after the screw removal, he fell again, complaining once again of severe pain in his hip. Plain radiographs were performed and a progressive abnormal position of the head of the hip with callus formation was seen. Initially the conservative treatment consisted of physiotherapy. Because of the persistence of disability he was referred to our orthopedic children's clinic several months later.

At that time he had a painful gait with a severely limited left hip function with 70 degrees of flexion. His left leg was externally rotated, with an internal and external rotation in extension of 0–30–50 degrees. The X-rays depicted a severe SCFE with a slip of 70 degrees and an open growth plate (Figure 2). Given the seriousness of the slip and the open growth plate, a re-(screw) fixation of the epiphysis was

performed with an additional subtrochanteric correction osteotomy (according to Southwick). The postoperative course was uncomplicated (Figure 3). After an initial period of six weeks of unloaded mobilization, weight bearing was supervised by the physiotherapist. During the last outpatient appointment, two years postoperatively, he was still found to be limping slightly, but he was pain free. On examination there was a leg length difference of 2 cm with a hip motion of 100 degrees of flexion and an internal and external rotation of 25–0–45 degrees. The Harris Hip Score was 97. The X-ray showed a cam lesion due to the deformity, no signs of avascular necrosis (AVN) or chondrolysis and a Southwick angle of 25 degrees.

Figure 1.
Patient 1. The X-ray of the left hip after *in situ* fixation.

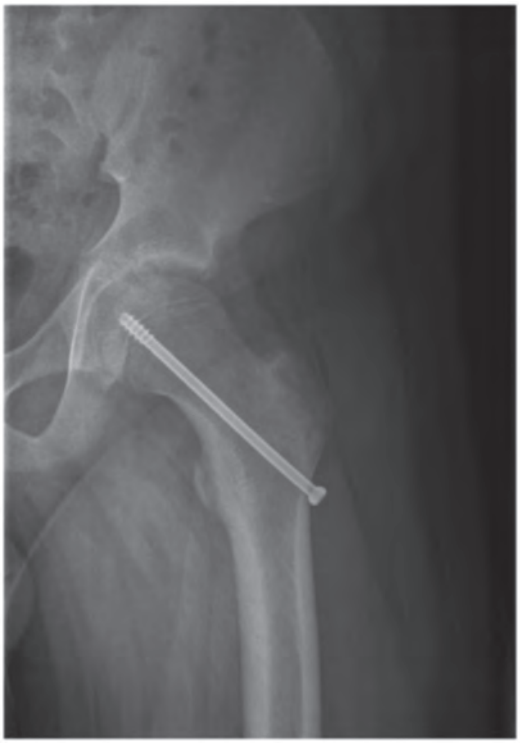


Figure 2.
Patient 1. The anteroposterior X-ray after removal of the screw fixation shows progression of the slip to nearly 70 degrees.

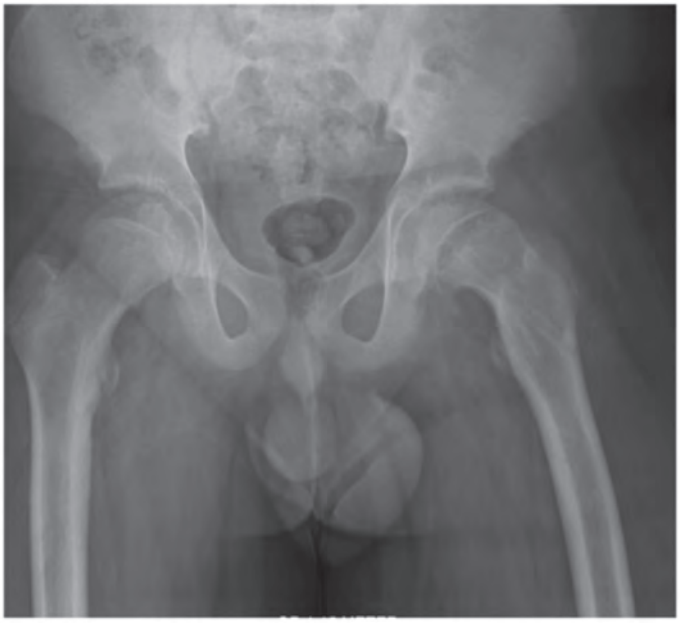
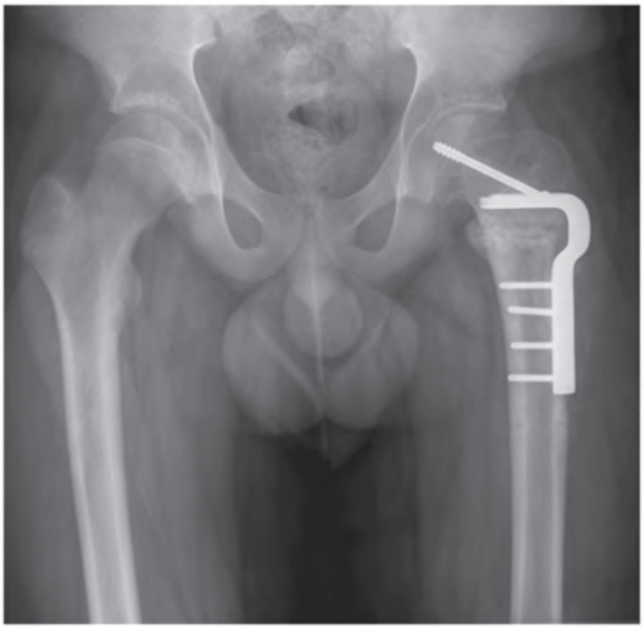


Figure 3.
Patient 1. The anteroposterior X-ray after the Southwick correction osteotomy with screw fixation of the head.



Patient 2

A 13-year-old girl was referred by her orthopedic surgeon to our orthopedic children's clinic. A year earlier she had suffered from pain in her left hip and knee after an injury whilst doing gymnastics. The general practitioner had requested only an anteroposterior radiograph of the pelvis, on which no abnormalities were seen. She was started on physical therapy, but pain nevertheless persisted. After referral to an orthopedic surgeon, a mild SCFE was diagnosed on the X-frog-lateral view. She was admitted and on the same day an *in situ* screw fixation was performed. The postoperative course was without problems, but once again her hip remained painful. X-rays depicted a good position of the femoral head, however, there was radiolucency around the screw. It was thought that the persisting pain might be explained by loosening of the screw and it was removed after four months.

The clinical course deteriorated after this procedure and she was referred to our clinic. She had a limping gait and a leg length discrepancy of 1cm. Flexion was limited to 100 degrees on functional assessment of the left hip, and internal and external rotation in extension was 20–0–45 degrees. X-rays demonstrated a moderate SCFE with an open growth plate. A progression of the slip to 50 degrees was present. We decided to perform a correction osteotomy according to Southwick with a re-screw fixation with one screw. Once again there was an initial period of six weeks of non-weight bearing. Her recovery was excellent, and after three months she was able to participate in gymnastics again. At final follow-up at 18 months postoperatively she was able to compete in sports and was almost pain free. On functional assessment, range of motion of the hip was unrestricted, with an internal and external rotation of 45–0–40 degrees. The Harris Hip Score was 96 and the X-ray showed a Southwick angle of 20 degrees and no signs of AVN or chondrolysis.

Discussion

SCFE is the most common hip disorder in adolescents with an incidence from one to seven per 100,000 [1]. The symptoms can range from a painful gait with minimal restrictions to a very painful condition with a non-weight bearing and an externally rotated leg. It is often (incorrectly) related to a minimal trauma. In case of preceding trauma however, it is essential to differentiate between SCFE and a transepiphysial fracture of the femoral neck. In SCFE the epiphysis becomes

weaker and eventually fails due to a combination of biomechanical and biological factors. A genetic component might possibly play a role [1,2]. Hip fractures, by contrast, are extremely rare in children or adolescents and are almost without exception always due to a high-energy trauma [3,4]. In these cases there is no pre-existing biological or mechanical weakening of the growth plate.

A radiological differentiation between the two entities can be difficult. For a proper radiological assessment a frog leg or lateral hip view is essential. In chronic or sub-acute SCFE, remodeling of the bone around the neck is often visible. However, an acute SCFE may have a radiological appearance similar to a transepiphysial fracture [5,6]. The long-term prognosis of SCFE is related to the severity of the initial slip. This is assessed by the method of Southwick on the frog leg or lateral radiograph [1,7]. In the case of a fracture, the Delbet Classification based on fracture location is used [5].

The main goal in the treatment of SCFE is to prevent further slippage and prevent complications such as AVN and chondrolysis. Conservative treatment is not indicated. In a mild to moderate slippage, *in situ* screw fixation is the gold standard [1]. Reduction attempts can cause AVN and are not indicated. However, in an acute or unstable slip, within 24 hours after the onset of symptoms, a tentative reduction attempt can be performed with *in situ* screw fixation [1,2,8]. The addition of a second screw provides only minimal gain in stability with an increased complication risk and is therefore not recommended [1].

If the pain and limping persists after screw fixation one should consider the presence of AVN, intra-articular screw penetration (with chondrolysis) or instability of the growth plate with progression of the slip. If problems arise from the screw fixation itself, it needs to be changed or reversed and not removed. In case of progression of the slip due to instability of the epiphysis a second screw can be added. The fixation must be secured until the growth plate closes to prevent further progression of the disease. Whether or not the material is subsequently removed remains controversial [9]. In the two presented cases the screw was removed with the idea that after a few months the epiphysis had achieved enough stability. However, with an open growth plate the underlying weakness is still present. Removal of the screw therefore causes further progression of the slip and deformity. In both cases, it had considerable consequences for the patient as an additional and more invasive procedure was required.

Treatment of an adolescent transepiphysial hip fracture consists of a closed or open reduction and screw fixation similar to that in SCFE. Removal of the osteosynthesis

material after consolidation of these fractures has never been reported and in case of any doubt it is advisable to leave the screw in place [3,4].

Conclusion

Early diagnosis and timely, adequate surgical stabilization is essential for a good outcome in SCFE. *In situ* fixation with one screw is standard treatment. The growth plate does not heal within several months and the original unstable situation persists until the growth plate is closed. Given the risk of progression of the slip, the fixation of the slipped epiphysis of the hip can only be removed after closure of the growth plate.

Consent

Written informed consent was obtained from the patients' legal guardians for publication of this case report and accompanying images.

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CHAPTER 9

Summary and general discussion.

Chapter 1

This thesis describes different aspects of slipped capital femoral epiphysis (SCFE). Although rare, SCFE is the most common adolescent hip disorder and may cause disability in young people and osteoarthritis in early life.

The general introduction presents the seven thesis aims. This thesis focuses on different aspects of SCFE such as the incidence in the Netherlands, it highlights the histopathological findings in the physis, the differences in treatments of acute SCFE used by Dutch and British pediatric orthopaedic surgeons and the operative outcomes of the Imhauser osteotomy simultaneously with a percutaneous screw fixation of the physes. Finally, the negative consequences of prematurely removing the percutaneous placed screw, i.e. before the end of the skeletal growth, are investigated.

Chapter 2

This chapter reviews the published literature concerning SCFE between 2008 and 2014. Based on this literature review, current concepts in SCFE are presented.

SCFE incidence has increased in Western and in Asian countries. Studies involving more detailed aspects of cellular processes are providing new insights into the pathogenesis of SCFE. There is an ongoing debate as to whether SCFE is more biomechanical or biochemical in nature, or a mixture of the two.

The treatment modalities of SCFE are discussed extensively in the literature. There are differences in SCFE treatment methods among and within countries, probably reflecting historical customs and mostly without empirical evidence. The standard treatment for stable SCFE is a single screw fixation. Despite extensive discussions in the literature, conclusions vary on: the treatment of unstable slip, treatment with different kinds of osteotomies, the necessity of contralateral percutaneous screw fixation, treatment of AVN and how to prevent femoro-acetabular impingement (FAI) which can lead to early osteoarthritis.

Chapter 3

The incidence of traumatic and non-traumatic SCFE (ICD9 code 820.01 en 732.2) in the Netherlands from 1998-2010 is assessed using data from the national hospitalization system of the Netherlands, and potential differences in sex ratios in SCFE are evaluated.

This chapter also reviews the present literature of the global incidence and gender differences. The most striking feature is an apparent global increase in incidence of

SCFE, probably due to an increase in the body mass index of adolescents. Despite a historical male dominance in SCFE incidence, there has been an increasing upward trend in female incidence in the Netherlands. This is also a global trend, but the Netherlands appears to be the first country showing similar SCFE incidence between sexes over the last decade.

Chapter 4

This chapter assesses the literature regarding the changes in hormonal balance in puberty and how this affects the physis related to SCFE. We focused on the role of hormones in possibly changing and potentially weakening the physes in SCFE and rendering the physes more vulnerable to forces acting upon them.

The focus is on the role of endocrine, metabolic and chronic diseases associated with SCFE. The physis in SCFE shows many histological differences with the normal physis in their columnar organisations, on a cellular level and in the extra cellular matrix (ECM). The fundamental problem is the lack of knowledge about the role each of these changes plays. It is unclear whether such changes are causal or adaptive, because the biopsies were taken after the slip had occurred. Major endocrine changes on the physis are active throughout puberty. The GH-IGF-1 axis has direct and indirect influences on the physis and is regulated by different hormones and growth factors. Sex steroids in puberty can cause delayed sexual maturation together with delayed physis closure, and both are present in SCFE patients. This creates a prolonged phase of weakness and makes the physis vulnerable to the effects of increasing load, mainly in the pre-existence of obesity. Given the two parameters of delayed physis closure and load bearing capacity, it seems likely that leptin influences SCFE. Leptin blood levels are higher in overweight children and can cause an increase in the width of the proliferative zone of the physes, as has been observed in SCFE patients. Thyroid hormones directly and indirectly affect the physis and may facilitate or delay closure at the end of puberty. As SCFE also occurs at the end of puberty, it could be possible that changes in the level of thyroid hormones disturb the closure of the physis. Another likely influence on SCFE is the mineralization of the bones. An association has been described with seasonal variation and thus, indirectly changes in vitamin D levels could play a role, which could interfere with the bone mineralization.

Chronic diseases in children cause growth-impairment via different mechanisms acting on the GH-IGF1 axis and thus potentially affect the physis. This is particularly true of children with chronic renal failure, where renal osteodystrophy can become

a severe complication, and physis abnormalities can appear similar to those that are observed in SCFE.
The most commonly affected hormones in endocrinopathies in studies specific to SCFE are thyroid hormones and the growth hormone. Consequently, recommendations would be to test for endocrine and metabolic changes in young children (< 10 and < 12 years of age for girls and boys respectively) and where young children fall within the tenth percentile for short stature.
In conclusion, SCFE is most likely the result of a multifactorial event during adolescence when height and weight increase dramatically and the delicate balance between the various hormonal equilibria can be disturbed. Currently, there are no screening or diagnostic tests available to predict patients at risk to SCFE.

Chapter 5

This chapter describes the histopathology of SCFE compared with controls. After gaining medical ethical committee (METC) approval, we performed 20 biopsies of the physis in SCFE. We compared these with 11 biopsies of normal physis taken during epiphysiodesis of the distal femur or proximal tibia with leg length differences and in different amputations (Syme, below knee and 6th toe). S100 (representativeness of the chondrocytes in physes), caspase (marker for apoptosis) and CD34 (receptor for capillary endothelial cells) were tested next to eight hormonal receptors that are important in puberty (Insulin like Growth Factor Receptor (IGHR), Growth Hormone Receptor (GHR), Estrogen Receptor α and β (ERαβ), Thyroid Receptor α and β (TRαβ), Androgen Receptor (AR) and Leptin Receptor (LR)). SCFE generally leads to perturbed architecture of the regular aligned structures in the physis but the normal phenotype of hypertrophic chondrocytes prevails. Neither alteration in apoptosis nor in vessel density was observed. Finally, no differences were observed in hormonal receptor expression of the eight hormonal receptors important in puberty.
In conclusion, we found no evidence for differential hormonal expression in SCFE, suggesting that the biomechanical factors are a more likely cause of SCFE.

Chapter 6

This chapter compared how pediatric orthopaedic surgeons from the WKO Netherlands and BSCOS United Kingdom generally diagnose and treat acute, unstable SCFE; Aims were to address differences and similarities between the two and to compare both with the approach of POSNA members in the USA.

A questionnaire was send to these members and the differences were assessed in different countries (NL and UK) of diagnosis and treatment of acute or unstable SCFE. Based on the results of the questionnaire and a similar POSNA study, all three countries agreed that acute or unstable SCFE should be treated within 24 hours. Contrarily, differences in reposition of the femoral head, prophylactic percutaneous screw fixation and removal of screw showed no consensus between pediatric orthopaedic surgeons either within a country or among countries.

Chapter 7

This chapter reports on the follow-up of patients with SCFE who had a one-stage procedure with screw fixation and a downgrading of the slip by an Imhauser femur osteotomy. The aim was to prevent early impingement by changing the angle of the head relative to the acetabulum. The outcome parameters were clinical and radiological examination as well as the Harris Hip Score (HHS).

In chronic slips, more operative modalities have been described. The predominant treatment for the mild stable group is a percutaneous screw fixation to prevent further slippage. In moderate and severe SCFE treatment, the literature discusses several different procedures: subcapital osteotomy (modified Dunn), subcapital osteotomy with a surgical dislocation (Ganz) and the intertrochanteric osteotomies, like the Imhauser or Southwick osteotomy.

In conclusion, subcapital osteotomy can lead to perfect anatomical reduction, but there is a high risk of development of avascular necrosis. In the intertrochanteric osteotomy, the slip will be downgraded mostly to a mild slip, but with no avascular necrosis and is mostly positive in the long-term. However, impingement "syndrome" (FAI) by the metaphysic bump (cam-lesion) can occur, possibly leading to osteoarthritis.

Chapter 8

This case-report concerns two patients who were mistakenly diagnosed as Salter Harris 1 fractures of the femoral head, rather than the correct diagnosis, SCFE. The direct treatment of the disorder followed an appropriate procedure, by inserting one percutaneous screw in the correct position. The removal of the screw after "healing", however, preceded closure of the physis. In both cases the SCFE process continued and the slips transformed into one moderate and one severe slip with associated complications. An Imhauser intertrochanteric osteotomy was required for the deteriorated function in both patients.

In conclusion, surgeons, general practitioners and physical therapists can misdiagnose SCFE. Thus, screw removal should not be performed before the end of skeletal growth.

Synopsis and future directions

What is currently known about SCFE and where should our future efforts be focused? SCFE is the most common hip-disorder in adolescents and yet its challenging presentation can make it hard to diagnose. What causes SCFE is unknown, but we know that it is either related to biochemical causes such as the biochemical changes associated with puberty and endocrine disorders or to biomechanical causes such as retroversion of the femoral head or obesity. Most likely a combination of these two will cause a load on the weak physis, which it cannot resist.

The incidence of SCFE has increased globally over the last decade, probably due to a general increase in the human body mass index (BMI). The increase of incidence in Asia may be indirectly attributable to a diet change.

Questions about the future of SCFE merit discussion, despite its future development being difficult to predict.

Early diagnosis and hence treatment of SCFE in children would reduce the severity of a slip. Incidences in a Western population are 10 in 100.000, making a screening programme impractical. However the incidence in obese children appears to be increasing. Possibilities are registering children with obesity (BMI > 25) and scheduling them for annual check-ups for symptoms of decreased hip mobility by general practitioners or health care professionals. Should we continue to work on prevention programs for obesity in children? It appears sensible given obesity is a cause of numerous other problems, like heart disease, diabetes, asthma and social discrimination.

Another possibility is trying to isolate the cause of SCFE at a cellular level. This would require additional studies. Current studies failed to detect abnormal hormonal receptors, which are active in puberty, in the physes in SCFE. The answers may be found in the extracellular matrix, in untested hormonal receptors, or in other pathways. The cause might never be found if we look at the physes after the slip has occurred. So should we take an extra step and explore the whole human genome in order to calculate the statistical chance of developing this disease? No previous hereditary link with SCFE has been found, however.

Diagnosing SCFE is difficult because primary healthcare providers sometimes have insufficient knowledge of this disease to detect it early. Patients with SCFE

are sometimes misdiagnosed as having a SH type 1 fracture and are treated accordingly. This maybe because of the low incidence of SCFE and its challenging presentation. Children can report pain in the upper leg or even anterior part of the knee, but actually it is referred pain from their hip. Hence, further education about SCFE and its symptoms are required.

Even if the cause was known, there is no consistent consensus for treatment of children with SCFE.

Pediatric orthopaedic surgeons should be encouraged to collaborate internationally to enhance the possibility of finding an optimal treatment for SCFE. In pediatric orthopaedic surgery we encounter many rare diseases with low prevalence and incidence. Collecting data of patients and appropriate treatment should be centralised in one registry. This would allow the monitoring of the various treatments used for SCFE within the registry and lead to a more efficient treatment for any given situation. Also, the existence of both short and long-term complications could be monitored like AVN, chondrolysis, FAI and osteoarthritis. Further questions that need to be asked entail the types of complications that develop in different patients and the reason for these?

Should we train more surgeons in advanced techniques of hip reconstruction, like the hip dislocation with subcapital osteotomy or should we use more 3D reconstruction techniques for preoperative planning? In these difficult operations one might consider centralisation of the techniques or operations considering the high levels of complication rates, which are highlighted in the literature. Should we further consider the treatment possibilities of hips affected by osteonecrosis or early arthrosis and salvage operations even, for example, by early total hip reconstruction? Is there a role for bisfosfonates or more modern medication that only inhibits osteoclasts? Currently there is no evidence that this medication is beneficial for children with SCFE.

Our primary, future objective is to improve the knowledge base for all different aspects of SCFE through further research and the collaboration of pediatric orthopaedic surgeons globally. This would ensure children suffering from SCFE are less likely to suffer from motion limitation or early osteoarthritis.

HOOFDSTUK 9

Samenvatting en algemene discussie.

Hoofdstuk 1

Dit proefschrift beschrijft verschillende aspecten van de afglijdende heupkop (slipped capital femoral epiphysis ofwel 'SCFE'). SCFE, hoewel zeldzaam, is de meest voorkomende heupstoornis bij adolescenten. Deze afwijking kan invaliditeit en artrose veroorzaken bij jonge mensen.

De algemene inleiding presenteert de doelstellingen van dit proefschrift. Dit proefschrift richt zich op verschillende aspecten van SCFE zoals: de incidentie in Nederland, de histopathologische bevindingen in de groeischijf, de verschillen in de behandeling van acute SCFE door Nederlandse en Britse kinderorthopeden en de operatieve resultaten van de Imhäuser osteotomie gelijktijdig met een percutane schroeffixatie van de groeischijven. Vervolgens is er een casereport geschreven over de negatieve gevolgen van het te vroeg verwijderen van de percutaan geplaatste schroef, dat wil zeggen vóór het einde van de groei van het skelet.

Hoofdstuk 2

Dit hoofdstuk bespreekt de gepubliceerde literatuur met betrekking tot SCFE tussen 2008 en 2014. Op basis van dit literatuuronderzoek worden de huidige concepten in SCFE gepresenteerd.

SCFE incidentie is toegenomen in zowel Westerse als in Aziatische landen. Studies met meer gedetailleerde aspecten van cellulaire processen geven nieuwe inzichten in de pathogenese van SCFE. Er is een voortdurende discussie of SCFE meer biomechanisch of biochemisch van aard is, of een gevolg is van beide.

De verschillende behandelingsmethoden van SCFE worden uitvoerig besproken in de literatuur. Er zijn verschillende behandelingsmethoden tussen, maar ook binnen landen, waarschijnlijk als gevolg van historische gewoontes en meestal zonder empirisch bewijs. De standaardbehandeling voor stabiele SCFE is een fixatie met een enkele schroef. Ondanks uitgebreide discussies in de literatuur verschillen de conclusies ten aanzien van: de behandeling van onstabiele slip, behandeling met verschillende soorten osteotomieën, de noodzaak van een percutane schroeffixatie contralateraal, behandeling van AVN en hoe femoro-acetabulaire impingement (FAI) voorkomen kan worden hetgeen kan leiden tot vroege artrose.

Hoofdstuk 3

De incidentie van traumatische en niet-traumatische SCFE (ICD9 code 820.01 en 732.2) in Nederland tijdens 1998-2010 worden beoordeeld aan de hand van gegevens uit het Landelijke Medische Registratie (LMR), PRISMANT-kubus

ziekenhuis statistiek systeem. Tevens worden de mogelijke verschillen in sekse in SCFE geëvalueerd en vergeleken met de populatie cijfers van het Centraal Bureau voor de Statistiek.
In dit hoofdstuk wordt eveneens de huidige literatuur besproken inzake de wereldwijde incidentie en gender verschillen. Het meest opvallend is een wereldwijde toename van de incidentie van SCFE, waarschijnlijk als gevolg van een toename van de body mass index (BMI) van adolescenten. Ondanks een mannelijke dominantie in de incidentie van SCFE beschreven in de literatuur is er een toenemende opwaartse trend in vrouwelijke incidentie in Nederland. Dit is ook een wereldwijde trend, maar Nederland lijkt het eerste land met gelijke SCFE-incidentie tussen mannen en vrouwen gedurende de afgelopen tien jaar.

Hoofdstuk 4
In dit hoofdstuk wordt de literatuur besproken met betrekking tot de veranderingen in de hormonale balans in de puberteit en hoe dit van invloed is op de groeischijven met SCFE. We hebben ons gericht op de rol van hormonen in het eventueel veranderen en mogelijk verzwakken van de groeischijven in SCFE en waardoor de groeischijven kwetsbaarder worden voor de krachten hierop.
De focus ligt op de rol van de endocriene, metabole en chronische ziekten die samenhangen met SCFE. De groeischijf in SCFE toont vele histologische verschillen met de normale in kolommen georganiseerde groeischijf, op cellulair niveau en in de extracellulaire matrix (ECM). Het fundamentele probleem is het gebrek aan kennis over de rol die elk van deze veranderingen teweegbrengt. Het is onduidelijk of dergelijke veranderingen causaal of adaptief zijn omdat de biopten werden genomen nadat de slipheeft plaatsgevonden. Belangrijke endocriene veranderingen op de groeischijf zijn in de gehele puberteit actief. De GH-IGF-1-as heeft directe en indirecte invloeden op de groeischijf en wordt geregeld door verschillende hormonen en groeifactoren. Geslachtshormonen in de puberteit kunnen vertraagde seksuele rijping veroorzaken samen met een late sluiting van de groeischijf. Beide zijn aanwezig in SCFE-patiënten. Hierdoor ontstaat een periode van zwakte en dit maakt de groeischijf kwetsbaar voor de effecten van toenemende belasting, vooral bij de aanwezigheid van overgewicht. Gezien de vertraagde sluiting van de groeischijf en de krachten waar de groeischijf bloot aan komt te staan, lijkt het waarschijnlijk dat leptine van invloed is op SCFE. Leptine bloedspiegels zijn hoger bij kinderen met overgewicht en kunnen een toename in de breedte van de proliferatieve zone van de groeischijven veroorzaken, zoals

is waargenomen bij patiënten met SCFE. Schildklierhormonen zijn direct en indirect van invloed op de groeischijf en kunnen sluiting van de groeischijf aan het einde van de puberteit vergemakkelijken of vertragen. Aangezien SCFE ook aan het einde van de puberteit voorkomt, kan het mogelijk zijn dat veranderingen in het niveau van schildklierhormonen de sluiting van de groeischijf verstoren. Een andere waarschijnlijke invloed op SCFE betreft de mineralisatie van de botten. Een verband is beschreven met seizoensgebonden variatie en daardoor kunnen indirecte veranderingen van vitamine D een rol spelen, die kunnen interfereren met de botmineralisatie.
Chronische ziekten bij kinderen kunnen leiden tot een groeistoornis via verschillende mechanismen die van invloed zijn op de GH-IGF-1-as en dus potentieel van invloed zijn op de groeischijf. Dit geldt vooral voor kinderen met chronisch nierfalen, waarbij renale osteodystrofie, afwijkingen in de groeischijf kunnen veroorzaken die vergelijkbaar zijn met afwijkingen die zijn waargenomen in SCFE.
In de literatuur over SCFE zijn de meest afwijkende hormonen schildklierhormonen en groeihormonen. Daarom zou het aan te bevelen zijn om, jonge kinderen met SCFE (<10 en <12 jaar voor meisjes en jongens, respectievelijk) en jonge kinderen die binnen het tiende percentiel voor korte gestalte vallen, te testen op de endocrinologische en metabole stoornissen.
Concluderend is SCFE hoogstwaarschijnlijk het gevolg van een multifactoriële oorzaak wanneer tijdens de adolescentie lengte en gewicht aanzienlijk toenemen en het delicate evenwicht tussen de verschillende hormonenverstoord kan raken. Momenteel is er nog geen screening of diagnostische test beschikbaar die het gevaar voor SCFE voor patiënten kan voorspellen.

Hoofdstuk 5

Dit hoofdstuk beschrijft de histopathologie van SCFE vergeleken met een controle groep.
Na goedkeuring van de medisch ethische commissie (METC), zijn 20 biopten genomen van de groeischijf in SCFE. Deze werden vergeleken met 11 biopten van normale groeischijven, die verkregen zijn tijdens epiphysiodesis van de distale femur of proximale tibia met beenlengte verschillen en in verschillende amputaties (Syme, onder de knie en 6e teen). S100 (representatief voor chondrocyten in groeischijven), caspase (merker voor apoptose) en CD34 (receptor voor capillaire endotheelcellen) zijn getest naast acht hormonale receptoren die belangrijk zijn in de puberteit (Insuline-achtige Groeifactor Receptor (IGHR), Groei Hormoon

Receptor (GHR), Oestrogeenreceptor α en β (ERαβ), Schildklier Receptor α en β (TRαβ), Androgene Receptor (AR) en Leptine receptor (LR)). SCFE leidt over het algemeen tot verstoorde architectuur van de kolom structuur in de groeischijf maar het normale fenotype van hypertrofische chondrocyten blijft hetzelfde. Geen verandering werd waargenomen bij apoptose of in vaatdichtheid. Ook werden geen verschillen waargenomen in hormonale receptor expressie van de acht hormonale receptoren die belangrijk zijn in de puberteit.
Tot slot vonden we geen bewijs voor afwijkende hormonale receptor expressie in SCFE, wat suggereert dat de biomechanische factoren een meer waarschijnlijke oorzaak zijn van SCFE.

Hoofdstuk 6

In dit hoofdstuk wordt vergeleken hoe de leden van de Werkgroep Kinderorthopedie Nederland (WKO) en BSCOS in het Verenigd Koninkrijk over het algemeen een acute, instabiele SCFE diagnosticeren en behandelen; om zodoende de verschillen en overeenkomsten tussen de twee landen te vergelijken en dit tevens te vergelijken met de POSNA leden in de Verenigde Staten.
Naar de leden in NL en UK werd een vragenlijst gestuurd om de verschillen te kunnen vaststellen in de diagnose en behandeling van acute of instabiele SCFE in de verschillende landen. Op basis van de resultaten van de vragenlijst en een soortgelijke POSNA studie was overeenstemming dat acute of instabiele SCFE binnen 24 uur dient te worden behandeld. Echter er was geen consensus tussen de kinderothopeden binnen een land of tussen eerder genoemde landen in het repositioneren van de heupkop, de profylactische percutane schroef fixatie en het wel of niet verwijderen van de schroef.

Hoofdstuk 7

Dit hoofdstuk beschrijft de follow-up van patiënten met SCFE die werden behandeld middels een one-stage procedure met een schroef fixatie en een verbetering van de ernst van de slip door een Imhäuser femur osteotomie. Het doel was om vroege impingement te voorkomen door de hoek van de kop ten opzichte van het acetabulum te veranderen. De uitkomsten waren gebaseerd op klinisch en radiologisch onderzoek, evenals de Harris Hip Score (HHS).
Bij chronische slip zijn meerdere operatieve behandelingen beschreven. De belangrijkste behandeling voor de milde stabiele groep is een percutane schroeffixatie om verder afglijden van de heupkop te voorkomen. In matige en

ernstige SCFE behandeling worden in de literatuur verschillende procedures beschreven: subcapitale osteotomie (gemodificeerd Dunn), subcapitale osteotomie met een chirurgische dislocatie (Ganz) en de intertrochantaire osteotomieën, zoals de Imhäuser of Southwick osteotomie.
Concluderend kan een subcapitale osteotomie leiden tot een perfecte anatomische positie van de kop, maar is er een grote kans op de ontwikkeling van avasculaire necrose. In de intertrochantaire osteotomie, zal de matige of ernstige slip meestal in ernst worden verminderd, maar zonder ontwikkeling van avasculaire necrose. Daarnaast is er een positief lange termijn resultaat. Echter impingement (FAI) door het metafysaire gedeelte (cam-laesie) kan optreden, wat kan leiden tot vroege artrose.

Hoofdstuk 8

De case-study betreft twee patiënten die ten onrechte werden gediagnosticeerd met Salter Harris 1 fractuur van de femurkop in plaats van de juiste diagnose SCFE. De behandeling van de aandoening betrof een passende procedure door één percutane schroef in de juiste positie te plaatsen. Het verwijderen van de schroef na genezing van de zogenaamde fractuur, voor de sluiting van de groeischijf was verkeerd ingeschat. In beide gevallen bleef het SCFE proces doorgaan en de slip verergerde tot een matige en een ernstige slip. Een Imhäuser intertrochantaire osteotomie was nodig in verband met de verslechterde functie van het heupgewricht.
Tot slot kunnen chirurgen, huisartsen en fysiotherapeuten een verkeerde diagnose stellen bij SCFE. Geadviseerd wordt dat het verwijderen van de schroef niet moet worden uitgevoerd vóór het einde van de skeletgroei.

Synopsis en toekomstige richtingen in onderzoek.

Wat is er tegenwoordig bekend over SCFE en waar moeten we ons in de toekomst op richten?
SCFE is de meest voorkomende heupstoornis bij adolescenten en de uitdagende presentatie maken het moeilijk de juiste diagnose te stellen.
De oorzaken van SCFE zijn tot op heden niet bekend, maar er is een verband met de biochemische veranderingen in de puberteit en endocriene stoornissen of biomechanische oorzaken zoals retroversie van de heupkop of obesitas. Waarschijnlijk veroorzaakt een combinatie van beide een belasting op de zwakke groeischijf, waaraan onvoldoende weerstand kan worden geboden.

De incidentie van SCFE is wereldwijd toegenomen gedurende de afgelopen tien jaar, waarschijnlijk te wijten aan een algemene verhoging van de BMI. De toename van de incidentie in Azië kan indirect worden toegeschreven aan een verandering van dieet.
De toekomstige ontwikkeling van SCFE is moeilijk te voorspellen maar verdient verdere discussie.
Vroege diagnose en behandeling van SCFE bij adolescenten zou de ernst van een slip verminderen. Incidentie in de westerse bevolking is ongeveer 10 op 100.000, derhalve zou een screenings programma onpraktisch zijn. De incidentie bij kinderen met overgewicht lijkt echter toe te nemen. Kinderen met obesitas (BMI> 25) zouden kunnen worden geregistreerd en men kan deze groep voor een jaarlijkse controle door huisartsen of beroepsbeoefenaren in de gezondheidszorg laten onderzoeken naar symptomen van verminderde bewegelijkheid van de heup. Moeten we blijven werken aan preventieprogramma's voor kinderen met overgewicht? Het lijkt verstandig niet alleen voor SCFE, maar ook aangezien obesitas een oorzaak is van tal van andere problemen, zoals hart- en vaatziekten, diabetes, astma en sociale discriminatie.
Een andere mogelijkheid is de oorzaak van SCFE te isoleren op cellulair niveau. Hier zijn aanvullende studies voor nodig. Huidige studies zijn niet in staat geweest om abnormale hormonale receptoren die in de puberteit actief zijn, op te sporen in de groeischijven van SCFE. Misschien kunnen antwoorden gevonden worden in de extracellulaire matrix, in ongeteste hormonale receptoren, of andere onbekende routes. De oorzaak is moeilijk te vinden als we kijken naar de groeischijven nadat de slip is opgetreden. Moeten we overwegen om een extra stap te nemen en het gehele menselijke genoom te onderzoeken om de statistische kans op het ontwikkelen van deze afwijking te kunnen berekenen? Tot nu toe is er echter nog geen erfelijk verband met SCFE gevonden.

Diagnose van SCFE is moeilijk omdat de primaire zorgverleners soms onvoldoende kennis van deze ziekte hebben om dit vroegtijdig op te kunnen sporen. Patiënten met SCFE worden soms verkeerd gediagnosticeerd met een SH Type 1 fractuur en worden op basis van deze diagnose behandeld. Dit is wellicht een gevolg van de lage incidentie van SCFE en de soms wat uitdagende presentatie. Kinderen kunnen pijn aangeven in het bovenbeen of zelfs voorste deel van de knie, waarbij het eigenlijk een uitstralende pijn betreft van de heup. Vandaar dat verdere voorlichting over SCFE en haar symptomen zijn vereist.

Zelfs als de oorzaak bekend was, is er geen consistente consensus voor de behandeling van kinderen met SCFE.
Kinderorthopeden zouden moeten worden aangemoedigd om internationaal samen te werken teneinde een optimale behandeling voor SCFE te kunnen bepalen. In de kinderorthopedie komen meer zeldzame ziekten voor met een lage prevalentie en incidentie. Het verzamelen van gegevens van patiënten en een passende behandeling dient te worden gecentraliseerd in een internationaal register. Dit zou de controle van de verschillende behandelingen voor SCFE mogelijk maken en leiden tot een efficiëntere behandeling voor elke afzonderlijke patiënt. Ook zou het voorkomen van zowel korte als lange termijn complicaties kunnen worden gecontroleerd, zoals AVN, chondrolysis, FAI en artrose. Andere vragen die moeten worden beantwoord betreffen het type complicaties die zich voordoen bij verschillende patiënten alsmede de oorzaak hiervan.
Moeten we chirurgen meer trainen in geavanceerde technieken van heup reconstructie, zoals de heup dislocatie met subcapitale osteotomie of moeten we 3D reconstructie technieken gebruiken om preoperatief te kunnen plannen? In deze moeilijke operaties zou men kunnen overwegen de technieken of operaties te centraliseren gezien de hoge mate van complicaties die worden genoemd in de literatuur. Moeten we nog rekening houden met de behandelingsmogelijkheden van heupen die beïnvloed zijn door osteonecrose of vroege artrose en salvage operaties zelfs, bijvoorbeeld door een vroege totale heup prothese te plaatsen? Is er een rol voor bisfosfonaten of meer moderne medicijnen die alleen osteoclasten remt? Op dit moment is er geen bewijs dat deze medicatie gunstig is voor kinderen met SCFE.

Het primaire, toekomstige doel is om meer kennis te vergaren over alle verschillende aspecten van SCFE door middel van verder onderzoek, internationale registratie en de samenwerking van kinderorthopeden wereldwijd te verbeteren. Dit zal leiden tot een lagere kans op bewegingsproblemen of vroege artrose bij adolescenten met SCFE.

Abbreviations

AP	Anteroposterior
AVN	Avascular Necrosis
BMI	Body Mass Index
BSCOS	British Society for Children's Orthopaedic Surgery
ECM	Extra Cellular Matrix
FAI	Femoro-Acetabular Impingement
FU	Follow Up
HHS	Harris Hip Score
LMR	Dutch National Hospitalization Registry
METC	Medical Ethical Committee
MRI	Magnetic resonance imaging
POSNA	Paediatric Orthopaedic Society North America
PSA	Posterior Sloping Angle
SCFE	Slipped Capital Femoral Epiphysis
SH fracture	Salter Harris fracture
THA	Total Hip Arthroplasty
WKO	Dutch Pediatric Orthopaedic Society

Curriculum Vitae

Melinda Witbreuk was born on 1 October 1966 in Enschede, the Netherlands. She graduated at Jacobus college in Enschede in 1985. Given the numerus fixus for medicine at the time she was not able to start her medicine study immediately and started dentistry at Rijksuniversiteit Groningen followed by a year Health Science at Radboud universiteit Nijmegen. Finally she started her medicine study at the Rijksuniversiteit Groningen in 1987 which she completed in 1992. She continued her internships at the Vrije Universiteit in Amsterdam from 1992 to 1995. In the meantime she did several electives in Italy, Belgium, Ivory Coast and Curaçao. In 1995 and 1996 she worked as a surgical SHO in Heemstede and Leiden. In 1997 she moved to Southampton were she worked as a SHO in orthopaedics. Thereafter she started a 2 year basic surgical training rotation in London. In 1998 she married Remko Eddes and in 1999 her daughter Nicci was born in London. In 2000 and 2001 she continued her research and work in London and became a Fellow of the Royal College of Surgeons (FRCS).

In 2001 she continued her surgical training in Haarlem (head dr. H.L.F. Brom) after which she continued her orthopaedic training at the Amsterdam Medical Centre (head prof. dr. R.K. Marti, prof. dr. C.N. van Dijk) and at Tergooiziekenhuizen Hilversum (head dr. G.H.R. Albers) in the Netherlands from 2002 until 2006. It was also during this period that her son Oscar was born in 2005 after which she went back to London for six months to work as a fellow pediatric orthopaedics in the Royal National Orthopaedic Hospital (head ms. D.M. Eastwood) in Stanmore. During 2006-2007 she worked as a fellow pediatric orthopaedics in Utrecht (head: prof. dr. R.M. Castelein). In 2007 she started as a pediatric orthopaedic surgeon at the VU University Medical Centre in Amsterdam (head prof. dr. B.J. van Royen).

Since 2008, Melinda has worked 2 weeks per year at Harapan Jaya, a rehabilitation centre for disabled children in Pematang Siantar in Sumatra, Indonesia.

Kroezeboom

A Kroezeboom is a tree, usually an oak, which indicates a boundary or junction. In the east of the Netherlands stones or trees were often used as boundary determination of the ash from which the fields were divided. In addition, the place was also used as a sacred place or place for jurisdiction. The Kroezeboom in Fleringen south of Tubbergen and north of Fleringen in the province of Overijssel is among the oldest trees in the Netherlands. It is estimated that between 1500 and 1600 the tree was planted as 'loakboom' or 'markeboom'. The oak is probably between 400 and 500 years old and therefor one of the oldest oak trees in the Netherlands.

Throughout its existence, several measures have been implemented to strengthen the tree and keep it afloat. In 1972 rods were implemented (also called sutures) that are visible in the photo. At the top of the crown storm tension anchors are attached which hold the crown parts in balance.