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 physis. 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 physis), 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 physis 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 physis 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
Slipped Capital Femoral Epiphysis 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.