

Ph.D Thesis

**A radiographic study of Legg-Calvé-Perthes disease
Risk factors for poor outcome and prevalence of hip dysplasia**

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LIST OF ABBREVIATIONS

AA	Acetabular index angle
ADR	Acetabular depth to width ratio
AP	Antero-posterior
CCHS	Copenhagen City Heart Study
CE angle	Wiberg's center-edge angle
FHEI	Femoral head extrusion index
HAR	Head-at-risk
HD	Hip dysplasia
JSW	Joint space width
LCP	Legg-Calvé-Perthes sygdom
LCPD	Legg-Calvé-Perthes disease
OA	Osteoarthritis
THA	Total hip arthroplasty

ENGLISH SUMMARY

This thesis is based on four clinical studies concerning LCPD and the associated radiographic changes in the hip joint from the time of diagnosis to adulthood.

The aims of the thesis were:

I. To evaluate whether severity of disease, age at onset, gender and presence of HAR signs were risk factors for poor radiological outcome after non-containment treatment of LCPD patients.

IIa. To evaluate whether patients with LCPD were more at risk of having radiographic hip OA than control subjects, and whether hips with Stulberg Classes III/IV/V femoral heads had an increased prevalence of OA compared with hips with Stulberg Classes I/II femoral heads.

IIb. To determine whether conservatively treated patients with LCPD had an increased prevalence of THA compared with gender- and age-matched control subjects, and if patients with Stulberg Classes III/IV/V femoral heads had an increased risk of THA compared with patients with Stulberg Classes I/II femoral heads.

III. To compare radiographic parameters in the affected and non-affected hip in children suffering from LCPD with those of a control group, and to evaluate whether the radiographic changes were present at the time of diagnosis or developed later.

IV. To evaluate the prevalence of HD in adult LCPD patients and describe radiographic parameters of the affected and the non-affected hips in adult LCPD patients compared with those of a control group.

Patients included in the current study were referred to The Community of Disabled in Kolding, Denmark from 1941 to 1962. All patients were treated by a Thomas splint regardless of gender, age at onset of the disease, unilateral or bilateral disease, and severity of disease. The splint was used from the time of diagnosis until the reconstitution stage of the disease appeared on the radiographs.

At the time of diagnosis, the CE angle and the AA were measured on AP pelvis radiographs. At the fragmentation stage of the disease, radiographs were classified according to the modified Herring lateral pillar classification system into Herring group A, B, B/C and C. Presence of the five HAR signs (lateral calcifications, metaphyseal cysts, a horizontal growth plate, lateral subluxation and Gage's sign) were noted.

At skeletal maturity, AP and frog-leg lateral view were classified according to the revised Stulberg classification system into Stulberg Class I, II, III, IV and V.

Radiographs of gender- and age-matched control persons were obtained from Kolding Hospital.

At follow-up in 2005-2006, all patients, except for patients who had deceased, emigrated or were lost to follow-up owing to lack of a personal identification number in the civil registration system, were invited to a radiographic examination. Weight-bearing standardised AP pelvic radiographs were obtained. In patients without THA, the JSW, CE angle, AA and FHEI were measured. For the estimation of THA in patients who were deceased or who did not want to participate at follow-up, data from the national Danish Hip Arthroplasty Register and the Registries of the National Board of Health were collected.

Radiographs of gender- and age-matched control persons were obtained from the CCHS.

Our study found that:

I. A higher Herring groups as well as age at onset of disease were significant risk factors for a poor Stulberg outcome. No statistically significant correlation between respectively gender and presence of HAR signs and Stulberg Class was shown.

IIa. LCPD patients have an increased risk of hip OA compared with a gender- and age- matched control group. Patients in Stulberg Class III/IV/V have an increased risk of OA compared with patients in Stulberg Class I/II.

IIb. The prevalence of THA in LCPD patients is increased compared with gender- and age- matched control persons. The risk of having THA is increased in Stulberg Class III/IV/V hips compared with Stulberg Class I/II hips.

III. In the affected hip of LCPD patients the femoral head changes at diagnosis occur in an acetabulum similar to a gender- and age-matched control group evaluated by the CE angle and AA, which secondarily becomes deformed. In the non-affected hip, the radiographic measurements are the same as in the gender- and age-matched control group at the time of diagnosis of the disease. However at skeletal maturity the parameters are significantly different in Stulberg Class III/IV/V compared with the control group.

IV. Adult LCPD patients have a significantly increased prevalence of HD in the affected hip regardless of Stulberg Class compared with a control group. In contrast, the prevalence of HD in the non-affected hip is similar to the control group. In the affected hip and in the non-affected hip in Stulberg Class III/IV/V the CE angle is decreased and the AA is increased compared with the control group.

DANISH SUMMARY (DANSK RESUMÉ)

Denne afhandling er baseret på fire kliniske studier omhandlende LCP og de radiologiske forandringer i hoftelæddet fra diagnosetidspunktet til voksenlivet.

Formålet med afhandlingen er:

I. At belyse om sværhedsgrad af sygdommen, alder ved debut, køn og tilstedeværelse af HAR tegn er prediktive for et dårligt radiologisk resultat efter 'non-containment' behandling af LCP patienter.

IIa. At belyse om patienter med LCP har en øget risiko for at udvikle osteoartrose i hoftelæddet sammenlignet med kontrolpersoner, og om patienter med hofter i Stulberg klasse III/IV/V har en højere prevalens af OA sammenlignet med patienter med hofter i Stulberg klasse I/II.

IIb. At belyse om konservativt behandlede patienter med LCP har en øget prevalens af total hoftealloplastik sammenlignet med en køns- og alders-matched kontrolgruppe, og om patienter i Stulberg klasse III/IV/V har en øget risiko for THA sammenlignet med patienter i Stulberg klasse I/II.

III. At sammenligne radiologiske parametre i den afficerede og ikke-afficerede hofte i børn med LCP med en kontrolgruppe, og at undersøge om de radiologiske forandringer er til stede på diagnosetidspunktet eller om de udvikles efterfølgende.

IV. At beskrive prevalensen af hoftedysplasi i voksne som tidligere har haft LCP og at sammenligne radiologiske parametre i den afficerede og ikke-afficerede hofte med en køns- og alders-matchede kontrolgruppe.

Patienterne som er inkluderet i dette studie blev set på Samfundet og Hjemmet for Vanføre i Kolding, Danmark mellem 1941 og 1962. Alle patienterne blev behandlet med en Thomas splint uanset køn, debutalder, unilateral eller bilateral sygdom, og sværhedsgrad af sygdom. Splinten blev brugt fra diagnosetidspunktet indtil rekonstitutionsstadiet af sygdommen kunne ses på røntgenoptagelser.

På diagnosetidspunktet målt CE vinklen og AA vinklen på AP røntgenbilleder af bækkenet. På fragmenteringsstadiet blev røntgenbillederne klassificeret i henhold til den modificerede Herring lateral søjle klassifikation i Herring klasse A, B, B/C og C. Tilstedeværelse af HAR tegn (laterale kalcifikationer, metafysære cyster, en horisontal vækstlinie, lateral sublaksation og Gage's tegn) blev noteret.

Ved skeletal modning blev røntgenbilleder optaget i AP og Lauensteins projektion klassificeret efter den reviderede Stulberg klassifikation i Stulberg klasse I, II, III, IV og V.

Der anvendtes røntgenbilleder af køns- og alders-matchedede kontrolpersoner fra Kolding sygehus.

Ved follow-up undersøgelse i 2005-2006 blev alle patienter, bortset fra patienter som var afdøde, emigrerede eller ikke kunne findes på grund af manglende cpr-nummer, inviteret til en radiologisk undersøgelse. Der blev foretaget vægtbærende, standardiserede AP røntgenoptagelser af bækkenet. Hos patienter uden THA målt ledspaltebredden, CE vinklen, AA vinklen og femoral head extrusion index. For estimering af THA hos afdøde patienter, eller patienter som ikke ønskede at deltage i follow-up undersøgelsen blev data fra Patient Registeret og Dansk Hofte Alloplastik Register indsamlet.

Der anvendtes røntgenbilleder af køns- og alders-matchedede kontrolpersoner fra Østerbro
Undersøgelsen: Osteoartrose studiet.

I dette studie fandtes at:

I. Stigende Herring klasse og debutalder er signifikante risikofaktorer for et dårligt Stulberg resultat. Der fandtes ingen signifikant sammenhæng mellem henholdsvis køn og tilstedeværelse af HAR tegn og Stulberg klasse.

Ia. LCP patienter har en øget risiko for OA sammenlignet med køns-og alders-matchedede kontrolpersoner. Patienter i Stulberg klasse III/IV/V har en øget prevalens af OA sammenlignet med patienter i Stulberg klasse I/II.

Ib. Prevalensen af THA i LCP patienter er øget sammenlignet med køns- og alders-matchedede kontrolpersoner. Risikoen for THA er øget for patienter i Stulberg klasse III/IV/V sammenlignet med patienter i Stulberg klasse I/II.

III. I den afficerede hofte hos patienter med LCP opstår forandringer i lårbenshovedet i en hofteskål som er tilsvarende hofteskålen hos en køns- og alders matched kontrolgruppe vurderet udfra CE vinklen og AA vinklen. Hofteskålen deformeres sekundært. I den ikke-afficerede hofte var de radiologiske parametre sammenlignelige med kontrolgruppen på diagnosetidspunktet. Ved skeletal modning var parametrene signifikant ændrede i Stulberg klasse III/IV/V hofter sammenlignet med kontrolpersonernes.

IV. Voksne LCP patienter har en signifikant øget prevalens af hoftedysplasi i den afficerede hofte uanset Stulberg klasse. I modsætning var prevalensen af hoftedysplasi i den ikke-afficerede hofte sammenlignelig med kontrolgruppen. I den afficerede hofte og den ikke-afficerede hofte i Stulberg klasse III/IV/V var CE vinklen reduceret og AA vinklen øget sammenlignet med kontrolgruppens.

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3. LIST OF PAPERS

Study I. Risk factors for poor outcome after non-containment treatment in Legg-Calvé-Perthes disease

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Study II. The need for total hip arthroplasty in Perthes disease –a long-term study

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Study III. Radiographic changes in the hip joint in children suffering from Perthes disease. A case control study

Accepted Jour Ped Orthop B, January 2011

Study IV. Prevalence of hip dysplasia in Legg-Calvé-Perthes disease. A case control study

Submitted

4. BACKGROUND

4.1 Historical review

In 1895 Röntgen discovered the X-rays which particularly in orthopaedics allowed a more precise diagnosis of conditions that had previously been lumped together under the broad headings of chronic infection, fracture and arthritis. In 1909 and 1910 four doctors independently published closely related descriptions of the condition that we now call LCPD. However, only three recognised that it was a non-tuberculous condition of the child hip. In 1909 Waldenström (81) described a disease which he called 'Der obere tuberculöse Collumherd'. Due to the fact that all these patients responded positively to tuberculin Waldenström regarded the disease to be a benign form of tuberculosis. Since the tuberculin skin test is limited due to false-positive results, technical difficulties in administering the test and errors related to subjectivity in reading the results (59), Waldenström might have avoided this misinterpretation having a control group.

The following year, 1910, the American Legg (47) described 'An obscure affection of the hip joint' which was based on five cases characterised by the subjects being five to eight years of age, and limping, with absence of pain, and absence of shortening of the leg. The radiological changes were described as flattening of the femoral head, shortening and thickening of the femoral head and a translucent area near the epiphyseal line. The Frenchman Calvé (4), described ten cases of 'pseudocoxalgie' where the clinical symptoms were chronic or sub acute pain in the joint, a limp and reduced mobility. The radiological signs were flattening of the epiphysis with two or more ossification centres, hypertrophy of the neck of the femur, and in some cases, coxa vara. The German, Perthes (56), called the disease 'Arthritis deformans juvenilis'. He also described the occurrence of a limp with or without joint pain and the radiological signs of flattening of the femoral epiphysis and subsequent deformation.

Now, a century after the reports of Legg, Calvé and Perthes, the etiology of the disease still remain unsolved as well as the radiological classification, prognostic factors, the methods of treatment and radiographic outcome of the disease are still disputed.

4.2 Legg-Calvé-Perthes disease

LCPD is an idiopathic juvenile avascular necrosis of the femoral head, which affects about one in 10000 children. LCPD occurs between two and 18 years of age, but most commonly in males between four and eight years. Males are affected four times more than females. Bilateral

involvement occurs in 10 to 15 per cent of patients which usually more than a year's interval between onsets.

The etiology of LCPD is unknown. Congenital or developmental alterations in the proximal femoral vascular circulation may make the circulation vulnerable to vascular compromise as well as to alterations in the coagulability of blood, with endocrine, metabolic disorders, smoking, diet and socio-economic status possible contributing factors (3, 26, 80). There may also be a genetic predisposition for LCPD. There are differences between genders and ethnic groups in addition to familial clustering (19, 24, 62, 78). Moreover, there is an increased rate of congenital anomalies among children with LCPD (85) as well as morphological changes in the acetabulum, particularly retroversion (17). One of current studies (Study III) contributes to this discussion.

The first sign of LCPD is usually recurrent pain and limping. At physical examination loss of internal rotation of the hip is the earliest sign, and abduction is nearly always limited. The diagnosis is usually made by conventional AP and frog-leg lateral view radiographs of the pelvis. The disease is divided into four stages: synovitis, necrosis or collapse, fragmentation and reconstitution (Table 1).

Table 1. The four stages of Legg-Calvé-Perthes disease

Stage	Duration	Pathology	Radiographic feature
Synovitis	Weeks	Synovitis Cartilagenous hypertrophy	Radiographs: May be normal Ultrasound: Joint effusion Bone scan: Reduced uptake in the femoral head MRI: Marrow necrosis, irregularity of the femoral head
Necrosis or collapse	6-12 months	Necrotic portions of the femoral head undergo collapse	Increased density of the femoral head
Fragmentation	1-2 years	Avascular bone is resorbed	Patchy deossification Deformation of the femoral head
Reconstitution	Years	Formation of new bone	Overgrowth resulting in coxa magna and widening of the femoral neck

4.3 Treatment

The management of LCPD is very controversial and no single treatment method has proven to be clearly superior for all children with LCPD. The treatment of LCPD includes various non-operative

modalities including physiotherapy, abduction brace, non-weight-bearing or traction combined with bed rest or use of a hip splint. Surgical treatment consists of soft tissue release, femoral varus osteotomy, pelvic osteotomies or a combination of these methods. Today, the aim of the treatment for LCPD is to obtain containment of the femoral head in the acetabulum and preservation of the range of motion of the hip. The methods used to achieve containment are either non-operative or operative.

Containment can be achieved non-operatively, but the treatment is prolonged and lack of compliance is a problem.

The advantages of surgical treatment are instant increased femoral head coverage within the acetabulum and decreased forces acting on the weight-bearing femoral head. The disadvantages are the possible persistence of femoral varus angulations, non-union of the osteotomy, trochanteric prominence, leg-length discrepancy, early closure of the femoral physis, and a second operation for fixator removal.

Most studies of LCPD treatment are retrospective and without any control group. There is a lack of uniformity concerning the selection of patients, indications for treatment, criteria for evaluation and age groups. To our knowledge, only two prospective studies exist which compare methods of treatment (29, 86) (Table 2). According to the report by Herring *et al* (29), the recommended treatment mode is easy to apply in the clinic, and this study also clarified the complications of surgery and the need for fixator removal. In the study by Wiig *et al* (86) the treatment mode depended on a two-group Catterall classification and the femoral head coverage which made the treatment mode more complicated to use compared with Herring's study (29).

Table 2. Comparison of prospective studies on patients suffering from Legg-Calvé-Perthes disease

Study	Herring <i>et al</i> (29)	Wiig <i>et al</i> (86)
Number of patients treated	1. Non-operative* (n=225) 2. Surgical * (n=120) * Each investigator used one treatment mode	Catterall 1 and 2: Physiotherapy (n=38) Catterall 3 and 4, <6 years, femoral head coverage >80%: Physiotherapy (n=*) Catterall 3 and 4, <6 years, femoral head coverage <80%: Non-operative treatment (n=*) or surgery (23)** Catterall 3 and 4, ≥ 6 years: Non-operative treatment (n=81) or surgery (n=71)** * In the group of children in Catterall 3 and 4, < 6 years 145 patients had non-operative

		treatment ** Each investigator used one treatment mode
Non-operative treatment	Symptomatic treatment, range-of-motion or brace	Physiotherapy or Scottish Rite abduction orthosis
Surgical treatment	Innominate osteotomy or femoral varus osteotomy	Femoral varus osteotomy
Complications of surgery	Pin migration (n=3) Loss of position of osteotomy (n=1) Superficial pin-track infections (n=3) Protrusion of fixation through femoral neck (n=1) Fracture distal to fixation plate (n=1)	
Later operations	Innominate osteotomy group: Removal of fixation pins (n=68, 100%) Femoral osteotomy: Removal of blade-plates (n=46, 88%)	
Recommendation	Herring A: Symptomatic treatment Herring B \leq 8 years: Symptomatic treatment Herring B $>$ 8 years: Surgical treatment Herring B/C \leq 8 years: Symptomatic treatment Herring B/C $>$ 8 years: Surgical treatment Herring C: No benefit from surgery	Catterall 3 and 4, $>$ 6 years: Femoral varus osteotomy

4.4 The Thomas splint

In the current study the patients were treated with a Thomas splint. The splint consists of a proximal oval ring padded with boiler felt and leather, which fits around the groin, using the ischial tuberosity as a pelvic support. This ring is attached by two iron rods to a smaller ring below. Aprons of leather are stretched across the two bars to support the limb (Figure 1). The Thomas splint does not fix the hip in a so-called contained position. It is an orthosis that reduces weight on the hip joint. In the most favourable cases, 50% of the weight can be conducted to the ground surface bypassing the hip joint (39). If leg length discrepancy were present when the Thomas splint was applied, a sole raise was used on the non-affected hip.

Figure 1. The Thomas splint.



Picture copied from http://commons.wikimedia.org/wiki/File:Thomas_splint.jpg

5. AIMS OF THE STUDIES

The aims of the studies were:

I. To evaluate whether severity of disease, age at onset, gender and presence of HAR signs were risk factors for poor radiological outcome after non-containment treatment of LCPD patients.

Ia. To evaluate whether patients with LCPD were more at risk of having radiographic hip OA than control subjects, and whether hips with Stulberg Classes III/IV/V femoral heads had an increased prevalence of OA compared with hips with Stulberg Classes I/II femoral heads.

Ib. To determine whether conservatively treated patients with LCPD had an increased prevalence of THA compared with gender- and age-matched control subjects, and if patients with Stulberg Classes III/IV/V femoral heads had an increased risk of THA compared with patients with Stulberg Classes I/II femoral heads.

III. To compare radiographic parameters in the affected and non-affected hip in children suffering from LCPD with a control group, and to evaluate whether the radiographic changes were present at time of diagnosis or developed later.

IV. To evaluate the prevalence of HD in adult LCPD patients and describe radiographic parameters of the affected and the non-affected hip in adult LCPD patients compared with a control group.

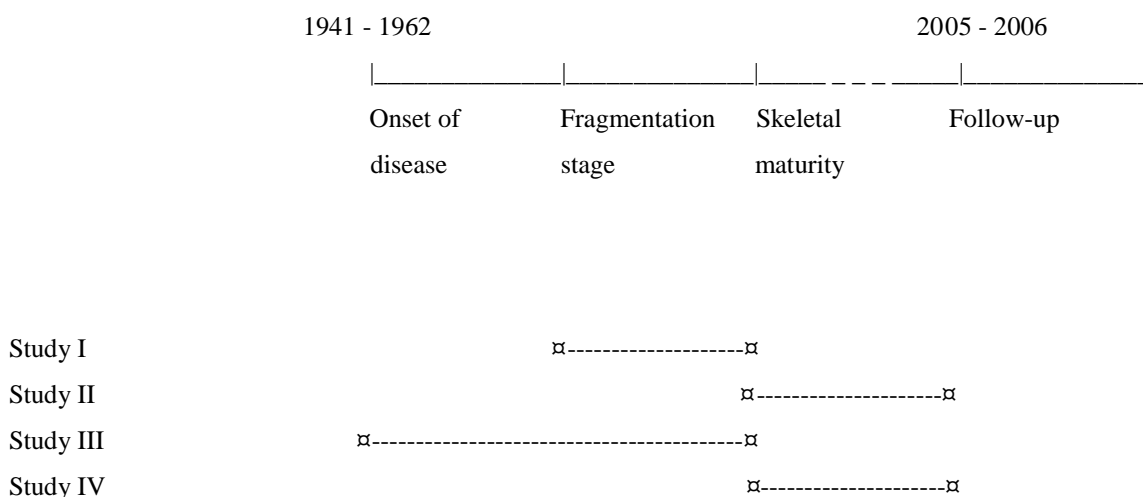
6. METHODOLOGICAL CONSIDERATIONS

6.1 Patients

The study cohort consisted of 167 patients (191 hips) registered in our archives who were suffering from LCPD. All patients were referred to The Community of Disabled in Kolding, Denmark from 1941 to 1962. One hundred and forty-three patients had unilateral and 24 patients had bilateral involvement. All patients were treated with a Thomas splint regardless of gender, age at onset of the disease, and severity of disease.

All patients were enrolled in this study. However, due to different inclusion and exclusion criteria in the papers and the varying time periods for the different studies, the number of patients might differ from one paper to another. A timetable for the studies is shown below (Figure 2).

Figure 2. Period of time for the studies



6.2.1 Control groups

It was considered unethical to take radiographs of healthy children; therefore a control group was obtained from gender- and age-matched children who had radiographs made of their pelvis due to a trauma or transient synovitis. The radiographs were obtained from Kolding Hospital from 2003 – 2009 and included patients with the following diagnosis: contusio coxae, contusio lumbales, laesio traumatica multiplex and transient synovitis. The ratio of LCPD patients to control persons was 1:1.

In order to be included in the control group radiographs had to be described without LCPD, osteomyelitis, fracture, epiphysiolysis, tumour and arthritis by a senior radiologist. The control persons were excluded if they had radiographic signs or laboratory finding indicating LCPD, osteomyelitis, tumour or arthritis within three months after they had transient synovitis. The tube-to-film distance was not standardised, however; since the radiographic measurements are measured in degrees the lack of standardisation does not influence the results. Some of the children having transient synovitis had an increased amount of fluid in the hip joint evaluated by ultrasound. This might lateralize the femoral head and thereby decrease the CE angle. However, there was no significant difference in the CE angle in the affected hip and the non-affected hip in those children. Moreover, no significant difference was present between the radiographic measurements in patients suffering from transient synovitis and trauma. Hence, we have no reason to believe that the CE angle in the control group was biased. AP radiographs of the pelvis were obtained from adult control persons from the CCHS; the Osteoarthritis sub-study. The CCHS is a longitudinal health survey of an adult, Caucasian cohort from the county of Österbro in Copenhagen, Denmark, recruited by a random social security algorithm. The radiographs were obtained in the standing position, feet pointing straight forward. Tube-to-film distance was 120 cm (36).

6.3 Classification systems

For a radiological classification and measure to be of prognostic value it must be possible to diagnose the sign reliably and it should be related to an accurate long-term prognosis. Catterall's and Salter-Thompson's classification systems are probably the most commonly used classification systems used to assess the severity of LCPD during the active phase of the disease and both use the extent of involvement of the epiphysis. The Catterall system has shown a poor inter- and intra-observer agreement (7, 27, 61, 79) whereas the association between the Salter-Thompson classification and outcome was reportedly good (51). However, Wiig *et al* (84) did not find good inter-observer agreement for the Salter-Harrison classification system. In addition, a subchondral fracture may be missed in many patients because it appears briefly and is seen in only a minority of patients (64). In 2004, Herring *et al* (28) introduced the modified lateral pillar classification and reviewed the Stulberg classification in order to get a reproducible classification. These classifications systems have been used in this research (Studies I-IV).

6.3.1 The modified Herring lateral pillar classification

The Herring classification is used as the prognostic indicator for deciding among treatments options ranging from conservative to surgical treatment, and the height of the lateral pillar is the major determinant of patient management. The advantages of the new classification systems include the simplicity of application, reliability with good inter- and intra-observer agreement and according to the modified pillar classification, high association with the outcome at skeletal maturity (1, 29). In the current study (Study I) the intra-observer reliability was almost perfect for the Herring group. The initial Herring classification can often be misleading with regard to outcome as further progression of the disease and collapse can occur (42). In this study (Study I), radiographs several months apart were studied, in order to choose the radiograph from the fragmentation stage, from which the modified Herring lateral pillar classification was made.

6.3.2 Stulberg's classification system

The classification system described by Stulberg *et al* (71) has frequently been used to classify the end result of patients suffering from LCPD (Table 3). Stulberg *et al* (71) described that patients having hips classified as Class I or II functioned essentially normally throughout adulthood; Class III and IV hips showed radiographic signs of OA when the patients were in their forties and fifties; and patients with Class V hips developed painful and disabling OA in early adulthood.

The intra- and inter-rater reliability of the classification system was called into question by Neyt *et al* (55) who found it to be 'marginally acceptable'. In 2004, Herring *et al* (28) reviewed the Stulberg classification and found it difficult to delineate the borderlines between groups. To improve the accuracy of the classification definitions were specified as shown in Table 3. The inter-observer agreement was almost perfect for the revised Stulberg classification in the current study (Study I).

Table 3. The original and revised Stulberg classification systems

Stulberg Class	The original Stulberg classification (71)	Stulberg classification revised by Herring <i>et al</i> (28)
I	A completely normal hip joint	A femoral head that cannot be distinguished from normal
II	A spherical femoral head (same concentric circle on AP and frog-leg lateral view) but with one or more of the following abnormal characteristics of the femoral head, neck, or acetabulum: (1) larger than normal femoral head, (2) shorter-than-normal	A round femoral head that fits within 2 mm on the same circle of both the AP and the frog-leg lateral radiographs

	femoral neck; or (3) abnormally steep acetabulum	
III	A non-spherical but not flat femoral head. Abnormal characteristics of the femoral head, neck, and acetabulum as described for Class II	An ovoid femoral head that does not fit within 2 mm of the circle on one or both radiographic views
IV	A flat femoral head and abnormalities of the femoral head, neck and acetabulum	A femoral head with at least 1 cm flattening of the weight-bearing area on one or both views
V	A flat femoral head and a normal femoral neck and normal acetabulum	A femoral head with collapse within a round acetabulum

6.3.3 Head-at-risk signs

In 1971, Catterall (5) described how the stage of LCPD at the time of diagnosis, the age of the patients, and the gender influenced the final outcome of the disease. He noticed that some of the patients had an unfavourable outcome even though these criteria promised otherwise and described four HAR signs associated with a poor prognosis; Gage's sign, calcifications lateral to the epiphysis, lateral subluxation and the angle of the epiphyseal line. The fifth HAR sign namely metaphyseal cysts, was described in 1982 (69).

The major problems regarding HAR signs are the use of different methods in measuring lateral subluxation (15, 25, 70), different definitions of Gage's sign (5, 22) and lack of a strict definition of a horizontal growth plate.

In the current study (Study I) the growth plate was defined as horizontal when the slope was more than 73 degrees (49). Lateral subluxation was present when less than 80 per cent of the femoral head was covered by the acetabulum (25). The intra-observer reliability in the current study (Study I) was almost perfect for the metaphyseal changes, horizontal growth plate and Gage's sign. The reliability regarding lateral subluxation was good whereas it was moderate for the lateral calcification.

In order to make sure that the presence of lesions was not due to differences in the radiographic quality, the lesions had to be present on two sequential radiographs.

6.4 Evaluation of osteoarthritis

The definition of radiographic hip OA varies throughout the literature as a combination of radiographic evidence of joint degeneration: osteophytes, subcondral sclerosis, subcondral cysts and

reduced JSW. In the current study we defined hip OA as a minimal JSW ≤ 2.0 mm on AP radiographs of the pelvis.

The Kellgren and Lawrence score and the Croft score are probably the most globally used radiological classification scores of OA. According to Kellgren and Lawrence (37) the following radiological features were considered evidence of OA: osteophytes, periarticular ossicles, narrowing of joint cartilage with sclerosis of subchondral bone, pseudocysts and altered shape of the bone ends. Presence of OA was divided into five grades: none, doubtful, minimal, moderate and severe. The inter-rater reliability was shown to be poor (6, 73) which might be due to the imprecise nomenclature.

In the study by Croft *et al* (10), male urograms were assessed with a tube-to-film distance of 100 cm as a standard AP view of the pelvis, but centred approximately 10 cm higher in the midline. The radiographs were graded from zero to five as shown in Table 4. Croft (10) found that the best radiological criterion relating to clinical symptoms of OA was the JSW. A JSW of ≤ 2.5 mm was associated with an increased prevalence of OA, and a JSW ≤ 1.5 mm was highly predictable of OA. The Croft grading is limited by the use of urograms which might underestimate minor structural changes compared with radiographs that are optimally exposed for the hip joint. Moreover the inter- and intra-observer reliability was shown to be poor (6, 73).

Table 4. The Croft score

Grade 0	No changes of osteoarthritis
Grade 1	Osteophytosis only
Grade 2	Joint space narrowing only
Grade 3	Two of osteophytosis, joint space narrowing, subchondral sclerosis, and cyst formation
Grade 4	Three of osteophytosis, joint space narrowing, subchondral sclerosis, and cyst formation
Grade 5	As in grade 4, but with deformity of femoral head

In the CCHS: the Osteoarthritis sub-study radiographs, of the pelvis were obtained standing, standardised and with known tube-to-film distance. Reports based on these patients showed that

extreme pelvic inclination during standing pelvic radiograph recording is a possible source of error in JSW measurements and described a significant association between a minimal JSW ≤ 2.0 mm and self-reported pain around the hip joint (33). Other studies have also reported a correlation of clinical hip OA and reduced JSW (10, 57). Measurements of JSW narrowing have shown higher reliability than other radiographic features in the hip joint as well as acceptable inter- and intra-observer agreement (30, 33, 40, 41, 73).

Previous studies (9, 48) have shown that JSW narrowing at the antero-superior and postero-inferior part of the hip joint is only seen at the faux profil view (oblique view) of the hip in the standing position. Lequesne *et al* (48) found three-quarters of patients with suspected hip OA, but no JSW narrowing on AP radiographs, had joint space narrowing on the faux profil view. In the current study (Study II) only AP radiographs were used to evaluate the prevalence of hip OA. Due to the lack of lateral radiographs of the lumbar spine to determine the pelvic inclination and lack of faux profil view, we might have misinterpreted the prevalence of OA.

Only the radiographic outcome, and not the clinical status of the patients, was evaluated in the current study (Study II). However, the JSW has shown a close association with actual clinical status and progression of degeneration (16, 33).

6.5 Hip dysplasia

Normal growth and development of the hip joint occur through a balanced growth of the proximal femur, the acetabular and triradiate cartilage and the adjacent bones (82). HD develops due to a mismatch in the normal containment of the femoral head in the acetabulum. Primary HD is a congenital or early developmental condition, while secondary HD might develop due to LCPD, congenital dislocation of the hip, or generalised conditions with neuromuscular affection such as cerebral palsy and Down's syndrome (8, 46, 66, 82).

The position of the femoral head to the acetabular cavity was assessed using the CE angle and FHEI. The acetabular anatomy can be assessed geometrically by the AA, the acetabular depth to width ratio (ADR) or ACM angle. Nelitz (54) reported a high correlation of inter- and intra-observer reliability for the CE angle, AA, FHEI and ADR, but not for the ACM angle. We omitted the ADR and ACM angle in hips from both adult and children, and FHEI in children because of poor intra-observer agreement in current study.

The CE angle is the most commonly used radiographic parameter in clinical and epidemiological studies on HD (83). The CE angle relates acetabular coverage to the position of the femoral head,

but does not indicate the shape of the femoral head or the shape and depth of the acetabulum. A clear-cut definition of cut-off values are based on arbitrary grounds with no correlation to the clinical status of patients. However, most authors agree that a CE angle in adults of less than 20 degrees is definitively dysplastic, and that a CE angle between 20 and 25 degrees is borderline dysplastic, while a CE angle more than 25 degrees is normal (13, 21, 53, 72, 77). Another widely used radiographic angle measure in HD is the AA describing the obliquity of the weight-bearing sclerotic zone of the acetabulum.

AP pelvic radiographs constitute the primary source material in epidemiological studies of HD. Radiographically the typical dysplastic hip has a shallow and wide acetabular cavity with an excessively oblique articulating dome, deficient anterior and lateral containment of the femoral head and a hypertrophied rim.

HD was evaluated on weight-bearing AP pelvic radiographs with a foramen obturator index of 0.7-1.8 as too much pelvic rotation might bias the measurements (34, 76). According to Jacobsen *et al* (34) inclination/reclination has a significant effect on measuring the CE angle. The inclination/reclination was measured as the distance between the symphysis and the sacrococcygeal joint however, the intra-observer agreement was poor and hence we were not able to make a reliable measurement of the inclination/reclination. The presence of HD in the current study was evaluated using the CE angle and AA (Study III, IV). For the adult hips, FHEI was also assessed (Study IV). These measurements complement each other and are easy to use in clinical and epidemiological studies.

As the hip joint is a complex three-dimensional structure, a two-dimensional plain radiography cannot fully delineate its morphology and an evaluation based solely on radiographs runs the risk of underestimating the degree of anomaly. However, since it was not considered ethical to ask the patients for CT scans, we have used radiographs to evaluate dysplastic changes in the LCPD patients. Likewise dysplasia in the control group was evaluated from radiographs and not CT scans.

7. DISCUSSION OF RESULTS

A century after the reports of Legg, Calvé and Perthes, the etiology, treatment, prognostic factors, radiological classification and radiographic outcome of LCPD are still disputed. The current study evaluated prognostic factors and radiographic outcome of patients treated without containment of the femoral head or surgery, but treated with only weight-relieving interventions and hence a course of the disease close or identical to the natural history of LCPD.

7.1 Risk factors for poor radiographic outcome at skeletal maturity

The radiographic outcome for LCPD patients at skeletal maturity has been described in numerous studies. Most of those studies are retrospective where inclusion criteria, classification of the disease and treatment of the patients varied considerably; hence it is difficult to draw firm conclusions on the recommendations for treatment. Only the studies by Herring *et al* (29) and Wiig *et al* (86) are prospective studies describing the outcome related to age, gender and severity of disease. They have several advantages: 1) All patients in the given time period suffering from LCPD are known, whether they were included or excluded from the study, 2) the radiographs are obtained at regular time intervals and 3) in Herring's study the patients were excluded if anything in their history indicated that the child may not suffer from LCPD. The results are presented in Table 5. In contrast, the cohort of patients in our study has been found retrospectively in our archives from 1941 to 1962; hence it is possible that we may have missed patients due to insufficient or wrong registration. Our patients had radiographs taken at four to seven months intervals. Therefore, we might have overlooked HAR signs or misclassified the patients into a Herring class that was too low. According to the still existing medical records, none of the patients suffered from conditions such as metabolic diseases.

Table 5. Comparison of prospective studies on patients suffering from Legg-Calvé-Perthes disease

	Herring <i>et al</i> (29)	Wiig <i>et al</i> (86)	Current study (Study I)
Study design	Prospective Multicenter	Prospective Multicenter	Retrospective
Number of patients enrolled	451 hips (uni- and bilateral)	368 hips (unilateral)	143 hips (unilateral)
Included	Initial stage of disease	All children with LCPD from	All children with LCPD from

	Children 6 to 12 years old at onset of disease	1996 – 2001 seen at hospital with paediatric orthopaedic services in Norway	1941 to 1962 treated at The Community of Disabled in Kolding, Denmark.
Excluded	N=459 Radiographic sign of re-ossification, hematologic disorder, history of steroid therapy, hypothyroidism, juvenile arthritis, diabetes, renal failure, any metabolic or neoplastic disease, a family history or radiographic findings of multiple epiphyseal dysplasia, hip infection, history of developmental dysplasia of the hip, failure to follow protocol, lost to follow-up, age <6 years or >12 years at onset of disease	N=57 Radiographic sign of re-ossification, bilateral disease, refused consent, lost to follow-up	N=69 Bilateral disease, missing or destroyed radiographs
Age	At induction: 7.98 years (6.0 – 12.0) (8.28 years females, 7.91 years males)	At onset of disease: 5.8 years (1.3 – 15.2) (5.9 years females, 5.8 years males)	At onset of disease : 6.2 years (2.7 – 12.8) (6.4 years females, 6.1 years males)
Ratio males : females	4 : 1	3 : 1	5 : 1
Treatment before inclusion	None	None	None
Number of hips at follow-up	345 hips	352 hips	74 hips
Age at final follow-up	16.6 years	Five years after onset	16 years
Radiographs evaluated	AP and Lauenstein projections At time of induction, 4, 8, 12 months and yearly thereafter	AP and Lauenstein projections At time of induction, 1, 3 and 5 years after diagnosis Patients undergoing osteotomy was also seen two months post-operatively	AP and Lauenstein projection. 4 to 7 months time interval
Radiographic	Revised Herring classification	1. Original Herring classification	Revised Herring classification

classification at onset	(A, B, B/C, C)	(A, B, C) 2. Two-group Catterall classification.	(A, B, B/C, C)
Radiographic classification at follow-up	Stulberg classification modified by Herring <i>et al</i> (28) Stulberg Class I and II outcome was combined. Stulberg Class IV and V outcome was combined	Stulberg classification modified by Neyt <i>et al</i> (55) Stulberg Class I and II outcome was combined. Stulberg Class IV and V outcome was combined	Stulberg classification modified by Herring <i>et al</i> (28) Stulberg Class I and II outcome was combined. Stulberg Class III, IV and V outcome was combined
Outcome related to age at diagnosis	Children ≤ 8 years had better outcome than children aged >8 years ($p=0.0001$)	Children < 6 years had better outcome than children aged ≥ 6 years ($p<0.0001$)	Children < 7 years had better outcome than children aged ≥ 7 years ($p<0.01$)
Outcome related to gender	Females > 8 years had worse outcome than males > 8 years ($p=0.004$) No difference between males and females ≤ 8 years ($p=0.77$)	No significant difference between males and females ($p>0.05$)	No significant difference between males and females ($p=0.07$)
Outcome related to Herring group	The lower the Herring group the better Stulberg outcome ($p<0.0001$)	The lower the Herring group the better Stulberg outcome ($p=0.001$)	The lower the Herring group the better the outcome ($p=0.03$)

7.1.1 Herring classification, gender and age at onset

In the study by Herring *et al* (29) patients suffering from unilateral and bilateral disease were included. In contrast, Wiig *et al* (86) and the current study (Study I) only included patients suffering from unilateral disease. Classifying bilateral disease poses a dilemma since the original height of the lateral pillar is unknown. If both hips are affected at the same time the original height of the lateral pillar is unknown which makes classifying imprecise. Hence, comparison with the non-affected femoral head is necessary.

According to Herring the threshold for a poor outcome is eight years (29), six years according to Wiig (86) and seven years in the current study (Study I). In Herring's study only children aged six years or older were included which results in a mean age of eight years at induction. In the study by Wiig (86) as well as our study (Study I) the children included are two years younger than in the study by Herring (29). This and the number of patients included might explain the difference in threshold.

Regarding gender, Herring *et al* (29) reported that females over eight years at onset had a worse outcome than males over eight years at onset, while Wiig *et al* (86) did not find any relationship between gender and outcome. No significant correlation between gender and radiographic outcome was found in the current study (Study I). However there was a tendency for the females to end up in a higher Stulberg Class than males. This might be explained by differences in age and ratio of gender in the three studies.

In the first year after inclusion in Herring's study (29); the children had four radiographs done. In contrast, patients had four radiographs taken in five years in Wiig's study (86) where the second radiograph was made one year after diagnosis. Previous reports have shown that further progression of the disease and collapse can occur until the fragmentation stage appears on the radiographs, which is from several months to a year after onset of symptoms (42, 79). Hence, it is possible that some of the patients in Wiig's study (86) are classified in a lower Herring class.

In Wiig's study, radiographs at inclusion were classified according to the original Herring classification and a two-group Catterall classification (86). The Catterall system has been used widely, but the results are difficult to reproduce in inter-observer trials (7, 27), though another study found acceptable inter-observer reliability when assessed by experienced examiners (84). In Herring's study (29) and the current study (Study I), the revised Stulberg classification has been used which has a good inter- and intra-observer reliability.

In Herring's study (29) and the current study (Study I), radiographs at skeletal maturity were classified according to the modified Stulberg classification system. In contrast, Wiig (86) classified the radiographs according to the Stulberg classification system modified by Neyt *et al* (55) five years after induction. At this point in time, 15 per cent of the patients had closure of one or both of the triradiate cartilages and 14% had closure of one or both of the femoral head physis e.g. a significant proportion of the children were skeletally immature when they were classified at follow-up and hence might end up in another Stulberg Class at skeletal maturity.

Even though the original Stulberg classification was revised, it still has limitations. In the report by Herring *et al* (28), the tube-to-film distance, and therefore the magnification of the radiograph, was not specified. This poses a source of error when the definition of Stulberg Class II and III depends on differences in millimetres, and one centimetre is used as borderline in Stulberg Class IV hips. Moreover, Herring *et al* (28) did not define a round acetabulum, which is used to distinguish between Stulberg Class IV and V hips. Despite the limitations, the kappa value in the current study (Study I) for intra-observer agreement was 0.93 and hence almost perfect.

Common to the three studies are: the lower the Herring group, the better the radiographic outcome and younger children at age of diagnosis have a better outcome than older children.

7.1.2 Head-at-risk signs

There has been some controversy about how important HAR signs are for the outcome. Metaphyseal cysts (5, 69), Gage sign (5), lateral subluxation (5, 15, 25, 32), calcifications lateral to the epiphysis (5, 15) and the angle of the epiphyseal line (5) have been thought to be related to a poor prognosis by some authors, while others have considered them of little importance (15, 25, 32, 49). In the current study (Study I), we were unable to show a significant correlation between either presence of a single HAR sign or the number of HAR signs. Thus we regard the HAR signs to be less useful in clinical practice.

Except for calcifications lateral to the ephiphysis (5) no studies have, to our knowledge, described at which stage of the disease the radiographic changes should be diagnosed and for how long they appear. As mentioned in the methodological considerations (section 6.3.3), previous reports have reported a considerable variation in the diagnosis of HAR signs. Moreover the inter- and intra-observer agreement has been questioned (12, 20). These issues might explain the controversy in the relation to the importance of the HAR signs.

7.2 Long-term results in conservatively treated patients

The long-term risk for hip OA and THA in conservatively treated LCPD patients has been described in a number of retrospective reports (23, 31, 32, 38, 45, 57, 60, 63, 71, 74, 87, 88). The treatments have been a combination of several treatments such as: bed rest with and without traction (31, 32, 38, 45, 60, 63, 71, 88), abduction splints (63, 71, 74), plaster (63), spica cast with and without weight-bearing (23, 31, 32, 38, 57, 71, 74), Thomas splint (60, 87, 88), sling (38) shoe elevation on the non-affected side, crutches (38, 71, 87, 88), wheelchair (38) or no treatment (23, 87).

Due to missing patients at follow-up as well as differences in follow-up period, definition of OA, use of classifications systems and treatment, it is difficult to draw firm conclusions on the long-term prognosis. However, common to the articles are: the older the person is at onset of the disease, the worse the radiographic outcome, and the greater the radiographic deformity at skeletal maturity, the greater the risk of OA.

7.2.1 Osteoarthritis

The overall prevalence of OA in Study II was seven per cent after 47 years. This is low when compared with 24% after 50 years in Lecuires' study (45) and 51% after 42-47 years in Stulberg's study (71). Lecuire's study (45) did not mention which radiographic projections were evaluated. In the study by Stulberg (71), AP and frog-leg lateral radiographs were evaluated. This is in contrast to our study where only AP radiographs were obtained. The difference in OA prevalence might be attributed to the differences in OA definition and the radiographic projections.

The overall prevalence of OA defined as a JSW ≤ 2.0 mm in current study (Study II) was four out of 54 (7%). Perpich (57) defined hip OA as a JSW less than 2 mm compared with the other hip. The prevalence of OA in his study was three out of 38 (8%). In Stulberg's study (71), the prevalence of severe JSW narrowing (JSW narrowing more than 75% of normal) was 17 out of 171 (10%). Thus, the overall prevalence of OA defined as JSW narrowing in those studies is in concordance with our results.

Regarding Stulberg subclasses and hip OA, the prevalence of hip OA in the current study (Study II) was one out of 42 hips (2%) in Stulberg Class I/II and three out of 12 (25%) in Stulberg Class III/IV/V (Table 6). Stulberg *et al* (71) reported that for patients in Stulberg Class I/II, two out of 32 (6%) in study group I aged 42.4 to 47.8 years at follow-up, and zero out of 37 (0%) in study group II aged 32 years at follow-up, had OA. For the patients in Stulberg Class III/IV/V in study group I, 48 out of 67 (72%), and in study group II, 16 out of 35 (46%), had OA (Table 6). In the study by Ippolito *et al* (32), the prevalence of OA after 25 years was zero out of 25 (0%) for patients with Classes I/II femoral heads and 17 out of 36 (47%) for those with Classes III/IV/V femoral heads (Table 6). In both studies, OA was defined as either narrowing of the JSW, presence of osteophytes, subchondral sclerosis, or subchondral cysts, which is in contrast to our study where OA was defined as a minimal JSW ≤ 2.0 mm.

Table 6. Prevalence of osteoarthritis in Stulberg Class I/II and Class III/IV/V

Study	Prevalence of OA Stulberg Class I/II	Prevalence of OA Stulberg Class III/IV/V	Age at follow-up/years
Stulberg (71) Study group I N=99	6% (2/32)	72% (48/67)	42.4 – 47.8
Stulberg (71) Study group II	0% (0/37)	46% (16/35)	32

N=72			
Ippoloti (32) N=61	0% (0/25)	47% (17/36)	21 – 61
Study II N=54	2% (1/42)	25% (3/12)	52 - 54

In the current study (Study II) 20 hips had LCPD-related THA. Preoperative radiographs were not available for 17 hips, and in three hips with preoperative radiographs, the JSW observed on AP radiographs of the pelvis was greater than 2.0 mm, and according to our definition, were without OA. Since we do not have faux profile view of the hips we might have underestimated the prevalence of OA in those patients (9, 48). However, due to hip pain, the surgeons found indication for surgery. Possible explanations for a painful hip could be: osteochondritis dissecans, labral tears and synovitis (14) as well as abnormal biomechanics, incongruence and secondary HD.

7.2.2 Total hip replacement

We included 156 hips in this part of the study (Study II), of which 20 (13%) had a THA. Due to emigration (n=6 hips) and lost to follow-up (n=24 hips), we excluded 30 hips. Given that all the excluded hips did not have a THA, the prevalence of THA would be 20 hips out of 186 hips (11%) compared with zero out of 312 (0%) in the control group. Other studies showed a prevalence of THA ranging from 0% to 24% (23, 31, 32, 38, 45, 57, 60, 63, 71, 74, 87, 88) with a follow-up time ranging from 19 years with none of the patients having THA to 50 years with 12 out of 51 (24%) of the patients having THA. The differences in prevalence of THA might be explained by differences in follow-ups and lack of sufficient registration.

In our study (Study II), we do not believe any patients were missed at follow-up in this part of the study owing to insufficient or incorrect registration since every operation performed in Denmark has been recorded under a unique personal identification number in The Register of the National Board of Health (75) and The Danish Hip Arthroplasty Register.

7.3 Radiographic changes in the hip joint

The prevalence of HD in the adult hip varies throughout the literature from 1% to 15% (11, 35, 68). This might be due to different cut-off values and parameters applied. Moreover, most epidemiological studies of residual HD in adults are based on urograms or colon radiographs (11, 43, 44, 68) and not on plain radiographs of the pelvis. An epidemiological estimate from the CCHS

cohort showed that the prevalence of unilateral HD defined as a CE angle ≤ 20 degrees was 3% - 4% and that HD is approximately equally distributed between genders (35).

To our knowledge, the prevalence of HD in LCPD patients has not previously been described but, as reported in the current study, is significantly increased in the affected as well as the non-affected hip compared with a gender- and age-matched control group (Study III, IV).

7.3.1 Affected hip - at diagnosis and skeletal maturity

In Study III, we evaluated the radiographs obtained at the time of diagnosis of the disease since we expected no secondary changes in the hip joint at that time. We found that the CE angle at the time of diagnosis of LCPD was significantly decreased in the affected hip regardless of Herring group. In contrast, the AA in the affected hip was normal compared with the control group.

In adult LCPD patients (Study IV), the prevalence of HD in the affected hip was increased compared with the control group. This suggests that the acetabulum is normal at the onset of disease and that the femoral head is lateralised due to synovitis or widening of the femoral head due to cartilaginous hypertrophy. This issue is supported by previous reports (18, 50, 58, 65, 67, 82) where changes to the femoral head occurred first and changes in the acetabulum followed due to remodelling of the bone.

In the presence of coxa magna, the radius enlarges and the centre of the femoral head moves laterally. In a lateral deficient acetabulum, this will decrease the CE angle as well as FHEI. In contrast, the measurement of the AA is independent of the presence of coxa magna. The increased prevalence of HD in LCPD patients could be explained by the presence of a deformed ovoid or flat femoral head or coxa magna. However, we also found that hips with a spherical head, both in Class I (without coxa magna) and in Class II (with coxa magna), were dysplastic. This suggests that HD is not only a result of coxa magna but is also due to a change in the acetabulum.

7.3.2 Non-affected hip - at diagnosis and skeletal maturity

We evaluated if the radiographic parameters in the non-affected hip were affected at the time of diagnosis of the disease (Study III). This was not the case. The prevalence of HD in the adult hip (Study IV) defined as a CE angle ≤ 20 degrees or an AA > 10 degrees, was the same as in the gender- and age-matched control group. However the CE angle was significantly decreased in adult hips from 33 degrees in the control group to 29 degrees in Stulberg Class III/IV/V. The AA was significantly increased from four degrees in the control group to seven degrees in Stulberg Class

III/IV/V hips. This suggests that the non-affected hip in severe cases might be influenced by the contra lateral hip.

There are some controversies about the pathogenesis of the non-affected hips morphology. Arie *et al* (2) has previously reported anterior and lateral flattening of the femoral head during the active phase of the disease, while Murphy *et al* (52) explains the radiographic changes as a consequence of the affected leg being shorter than the non-affected leg causing increased adduction of the femoral head and thereby, less acetabular coverage. The clinical consequence and the etiology of this finding are unsolved.

8. CONCLUSION

I. A higher Herring groups as well as age at onset of disease were significant risk factors for a poor Stulberg outcome. No statistically significant correlation between respectively gender and presence of HAR signs and Stulberg Class was shown.

IIa. LCPD patients have an increased risk of hip OA compared with a gender- and age- matched control group. Patients in Stulberg Class III/IV/V have an increased risk of OA compared with patients in Stulberg Class I/II.

IIb. The prevalence of THA in LCPD patients is increased compared with gender- and age- matched control persons. The risk of having THA is increased in Stulberg Class III/IV/V hips compared with Stulberg Class I/II hips.

III. In the affected hip of LCPD patients the femoral head changes at diagnosis occur in an acetabulum similar to a gender- and age-matched control group evaluated by the CE angle and AA, which secondarily becomes deformed. In the non-affected hip, the radiographic measurements are the same as in the gender- and age-matched control group at the time of diagnosis of the disease. However at skeletal maturity the parameters are significantly different in Stulberg Class III/IV/V compared with the control group.

IV. Adult LCPD patients have a significantly increased prevalence of HD in the affected hip regardless of Stulberg Class compared with a control group. In contrast, the prevalence of HD in the non-affected hip is similar to the control group. In the affected hip and in the non-affected hip in Stulberg Class III/IV/V the CE angle is decreased and the AA is increased compared with the control group.

9. FUTURE STUDIES

In the future it would be interesting to evaluate the outcome at skeletal maturity of patients we treat today with respect to clinical status as well as radiographic findings. Moreover the long-term risk of developing OA, the need for THA and the clinical status of patients treated today is even more interesting. Further prospective studies are needed to clarify these issues.

The prevalence of THA in LCPD patients in this thesis is increased compared to a control group. Evaluation of preoperative radiographs and clinical status for those patients might contribute to clarify the indication of THA.

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11. PAPERS

11.1 Risk factors for poor outcome after non-containment treatment in Legg-Calvé-Perthes disease

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Abstract

Objective: The purpose of this study was to evaluate prognostic risk factors related to a poor radiologically outcome.

Methods: The study consisted of 74 patients with Legg-Calvé-Perthes disease treated by a Thomas splint. The modified Herring lateral pillar classification and the reviewed Stulberg classification system was applied.

Results: A significant correlation between Herring group and Stulberg was found ($p=0.03$). There was a significant correlation between age at onset of the disease and Stulberg outcome ($p=0.05$).

Conclusions: The Herring classification correlated to the Stulberg outcome. Age of seven years or more at onset was risk factor for a poor Stulberg outcome.

Introduction

The goal of treatment in Legg-Calvé-Perthes disease (LCPD) is to create a congruent hip joint without deformity at the time of skeletal maturity in order to gain normal function and in the long term to reduce the risk of secondary osteoarthritis and total hip replacement. Present treatment of LCPD patients aims to achieve containment of the femoral head and include physical therapy, bracing/casting, adductor tenotomy and femoral and/or pelvic osteotomy. Decision regarding when and how to treat relies on a classification which is related to an accurate long-term prognosis. Furthermore, prognostic risk factors as age at onset, gender and presence of head-at-risk (HAR) signs should also be taken into account. Since most of the literature consist of studies where inclusion criteria, classification of the disease and treatment of the patients varied considerably, it is difficult to draw firm conclusions regarding prognostic factors and the natural course of the disease. The present study describes a group of LCPD patients treated conservatively in a non-containment weight-relieving manner [1], regardless of their gender, age at onset, presence of HAR signs and severity of disease.

The purpose of the study was to evaluate whether severity of disease, age at onset, gender and presence of HAR signs were risk factors for poor radiological outcome after non-containment treatment of LCPD patients.

Methods

Study population

From 1941 to 1962, a cohort of 167 patients with LCPD was treated at The Community of Disabled in Kolding, Denmark. According to the still existing medical journals, all patients were treated by a Thomas splint regardless of gender, age at onset of the disease and severity of disease. The Thomas splint is regarded as a non-containment treatment and reportedly reduces load on the hip [1]. The splint was used from time of diagnosis and until the reconstitution stage of the disease appeared on the radiographs, a mean of 26 (SD 8) months. The splint was used all day except for swimming and bathing. If leg length discrepancy was present when the Thomas splint was applied, a sole raise was used on the non-affected hip. None of the patients had surgery and to our knowledge no patients were referred to other hospitals. 143 patients had unilateral involvement and 24 patients had bilateral involvement.

Bilaterally affected patients were excluded, since Herring lateral pillar classification requires a normal contralateral hip to measure the original height of the lateral pillar. Patients with missing or destroyed radiographs were also excluded. Thus, 74 patients were included.

Excluded patients

The 69 patients excluded did not differ compared to the included patients regarding gender, age at onset of disease and duration of treatment with the Thomas splint (Table 1)

Prognostic risk factors-

Herring group. Anteroposterior radiographs during the fragmentation stage of the disease were classified according to the modified Herring lateral pillar classification into Herring group A, B, B/C and C [2]. Radiographs with several months apart were studied, and the radiograph showing the greatest lucency of the lateral pillar was chosen for classification.

Age at onset and gender. Retrospectively, the medical records of the patients were retrieved and gender, age at onset and duration of treatment with a Thomas splint were registered. Onset of disease was defined at the time when the patient started limping or complained of pain in the hip, thigh or knee.

Head-at-risk signs. The HAR signs include lateral calcifications, metaphyseal cysts, a horizontal growth plate [3] (Fig. 1), lateral subluxation (Fig. 2) and Gage's sign [4]. When the slope of the growth plate was more than 73 degrees it was defined as horizontal [3]. Lateral subluxation was

present when less than 80 per cent of the femoral head was covered by the acetabulum [5]. In order to make sure that the presence of lesions was not due to differences in the radiographic quality, the lesions had to be present on two sequential radiographs.

Stulberg classification

At skeletal maturity supine anteroposterior and frog-leg lateral radiographs of the pelvis and the hips were classified according to the reviewed Stulberg's classification system. Stulberg class I and II have a spherical femoral head, and class III, IV and V have a non-spherical or flat femoral head [2]. Since some of the patients had their gonads protected, it was impossible to make an Oxford grading of e.g. the junction of the ischial and pubic rami [6]. In contrast the triradiate cartilage and femoral head physis were visible in all of the radiographs. We therefore defined skeletal maturity when closure of the triradiate cartilage and closure of the femoral head physis had occurred on the non-affected hip.

Intra-observer agreement

Intra-observer reliability was assessed by blinded re-reading of a subset of 20 radiographs four months after the first reading.

For re-evaluation of Herring group and HAR signs ten radiographs were randomly selected from the group of radiographs primarily classified as either Herring group A or B, and ten radiographs from the group classified as Herring group B/C or C.

For re-evaluation of Stulberg class half of the randomly selected radiographs were primarily classified as having a spherical femoral head and the other half as having a non-spherical femoral head.

All radiographs were evaluated by the same author (LF).

Normality test, by probit plots, showed that all data were normally distributed. Thus data are presented as means with standard deviation [SD] in brackets.

To evaluate whether there was statistical significant differences between the study group and the group of excluded patient's, the t-test was used. For evaluation of prognostic factors on Stulberg outcome, all variables were analysed using gamma correlation coefficients. Intra-observer reliability was assessed using the weighted kappa coefficient. A kappa of 0.21 to 0.40 is considered to be fair; 0.41 to 0.60 moderate; 0.61 to 0.80 good and 0.81 to 1.0 almost perfect [7].

All statistical analyses were performed with the STATA version 10.0 statistical software. A significance level of $p < 0.05$ was chosen for all calculations.

Results

Seventy-four patients were included in this study. Their distribution in Herring group and Stulberg class is shown in Table 2.

Prognostic risk factors

Herring group. There was a correlation between Herring group and Stulberg outcome ($p = 0.03$ 95% CI 0.03-0.61) (Table 3). Thus, patients classified in a severe Herring group had an increased risk for ending up with a non-spherical or flat femoral head as seen in the more severe Stulberg class.

Age at onset. There was a correlation between age at onset of the disease and Stulberg outcome ($p = 0.05$ 95% CI 0-0.40), hence early onset of the disease resulted in a better Stulberg outcome (Table 3). Supplementary analysis of age at onset versus Stulberg outcome showed that the outcome in children younger than seven years at onset was significant better than in those aged seven years or more ($p < 0.01$ 95% CI -0.78-(-)0.13).

Gender. There was no significant difference in the number of boys (64%) and girls (62%) who was classified as Herring group A or B, compared to patients classified as Herring group B/C or C. There was a tendency for the girls to end in a more severe Stulberg class than the boys ($p = 0.07$, 95% CI -0.02-0.78) (Table 3).

Head-at-risk signs. Neither the presence of a single HAR sign (Table 3) nor the presence of more than one sign was correlated to a poor Stulberg outcome ($p = 0.21$, 95% CI -0.10-0.45) (Table 3).

Intra-observer agreement

The intra-observer reliability was almost perfect for the Herring class, metaphyseal changes, horizontal growth plate, Gage sign and Stulberg group. The reliability regarding lateral subluxation was good whereas it was moderate for the lateral calcification (Table 4).

Discussion

Even though prognosis and indication for treatment of patients with LCPD recently have been more clearly delineated [8], uncertainty still persists about the natural course of LCPD. The prevalence of total hip replacement and osteoarthritis in this cohort of patients nearly 40 years after onset of disease have recently been described [9].

This study was performed in order to evaluate risk factors for poor radiographic outcome in a uniform conservatively treated group of LCPD patients. Since the Thomas splint only reduces weight of the hip joint [1], we consider the results in this study, close or identical to the natural history of the disease [10].

The strength of the study is firstly, that the patients had an identical non-containment treatment with a Thomas splint regardless of degree of femoral head involvement, age at onset, gender and presence of HAR signs. The patients excluded did not differ from the patients included in the study. Secondly, the distribution of hips in Herring group A and B, and B/C and C are similar to the study by Herring *et al* indicating no bias in the material for severity of the disease [8]. Thirdly, the modified Herring lateral pillar and the reviewed Stulberg classification systems were used, which both have been shown to be reliable classification systems [2]. The most commonly used classification systems are probably the classification system by Catterall and Salter-Thompson. However; previous reports have show a poor inter- and intraobserver agreement for the Catterall system [11, 12, 13, 14]. Mukherjee [15] found a good correlation between the Salter-Thompson classification and outcome, which however not could be verified by Wiig *et al* [16]. In addition the subchondral fracture may be missed in many patients, because it is a transient phenomenon and is seen in only a minority of patients [17]. The advantages of the modified Herring lateral pillar and the reviewed Stulberg classification systems include the simplicity of application, reliability with good inter- and intraobserver agreement and according to the modified pillar classification, high correlation with the outcome at skeletal maturity [8]. We found almost perfect agreement with intra-observer kappa values of 0.89 and 0.93 for the modified Herring and Stulberg classification system, respectively.

A recent study by Forster *et al* [18] showed that the intra-observer reliability was good for lateral subluxation and metaphyseal cystic changes, moderate for lateral calcifications, and fair for Gage's sign and horizontal growth plate, whereas the inter-observer reliability in the diagnosis of HAR signs showed considerable variation. In contrast, DeBilly *et al* [19] found that lateral subluxation was the only HAR sign to have a poor inter-observer reliability. The major problems regarding

HAR signs are the use of different definitions of Gage's sign [4, 20], lack of a strict definition of a horizontal growth plate and different methods in measuring lateral subluxation [5, 21]. Green *et al* [5] found that when the extrusion of the femoral head exceeded 20% the chance of a good result was only 15%. We therefore choose to define lateral subluxation when less than 80% of the femoral head was covered by the acetabulum. In this study, there was acceptable intra-observer reliability in the diagnosis of the HAR signs, except the presence of lateral calcification.

Our study does also have some limitations. Firstly the study is based on radiographic findings and the clinical status of the patients has not been evaluated. Secondly our study is retrospective. Even though all patients in our archives diagnosed with LCPD from 1941 to 1962 are included, it is possible that we have missed patients due to insufficient or wrong registration. Thirdly, our study comprises of a small number of patients. We excluded five patients bilaterally affected and 69 patients with unilateral involvement due to insufficient or destroyed radiographs. Thus 74 patients out of 167 patients (44 %) were included.

The present study showed that as the degree of involvement of the lateral pillar increases, the risk for a poor Stulberg outcome increase as well. Thus our results support those who noted that the lateral pillar classification predicts the severity of the radiographic outcome [8, 20, 22].

Age at onset of the disease has been suggested as a strong predictor for outcome. The exact chronological age at which a poor prognosis is expected varies from five to eight years at onset [8, 23]. The majority of patients in our study with age at onset less than seven years (57%) and aged seven years or older (81%) were classified as Herring group A or B. Even though the majority of children less than seven years at onset had more involvement of the lateral pillar than children seven years or older, the Stulberg outcome was better for the younger children.

It has been stated that girls with LCPD have worse outcome than boys. This might be explained by the fact that girls reach skeletal maturity earlier than boys and accordingly have a shorter time for remodelling of the femoral head [8, 24]. In this study boys and girls have a similar age at onset, and no significant difference was present between girls and boys with respect to distribution in Herring group A and B, and B/C and C. No significant difference was found between gender and Stulberg outcome however, there was a tendency for girls to end in a more severe Stulberg class than the boys. In the prospective study of Wiig *et al* [22] they found no relationship between gender and a poor outcome, in contrast to the prospective study of Herring *et al* [8].

The HAR signs have been associated with a poor prognosis. Since some of the HAR signs may be uncertain as prognostic indicators [18, 19] and since we were unable to show a significant

correlation between HAR signs and Stulberg outcome, we regard the HAR signs to be less useful in clinical practise.

In conclusion, this study support the literature showing that age at onset of disease and increasing Herring class were significant risk factors for a poor Stulberg outcome.

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Figure 1. Horizontal growth plate. The slope of the growth plate is determined by measuring the angle between the femoral shaft and the epiphysis. The femoral shaft axis is defined by bisecting the femoral shaft at two points (D and G) and connecting these points. The epiphyseal axis is defined by locating two points (A and B) at the lateral and medial border of the epiphysis and connecting them. When the slope of the growth plate was more than 73 degrees it was defined as horizontal.

Figure 1

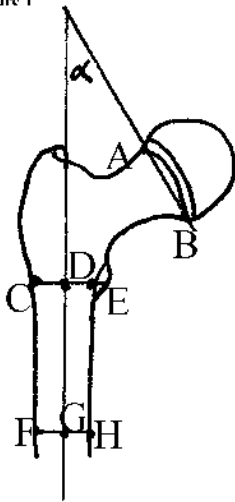


Figure 2. Lateral subluxation was measured as the percentage of the femoral head medial to Perkins' line (a-b) in relation to the width of the femoral head (a-c) ($ab/ac \times 100$). Lateral subluxation was present when less than 80 per cent of the femoral head was covered by the acetabulum.

Figure 2

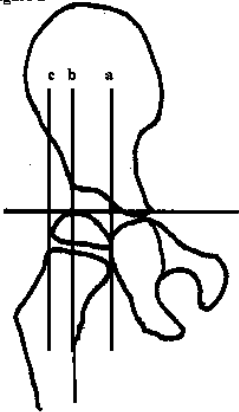


Table 1. The cohort consisted of 143 unilateral LCPD patients treated with a Thomas splint. Included and excluded patients are described. Age and time of treatment with a Thomas splint are presented as means and standard deviation in brackets.

	Included n=74	Excluded n=69	p-value
Ratio of girls:boys	1 : 4.7	1 : 4.3	0.85
Age at onset girls (years)	6.4 [2.7]	5.2 [2.2]	0.38
Age at onset boys (years)	6.1 [2.7]	6.5 [2.7]	0.38
Affected hip right/left (per cent)	47/53	48/52	0.95
Treatment with a Thomas splint (months)	26 [8]	24 [9]	0.22

Table 2. Relationship between Herring group and Stulberg class of the 74 included LCPD patients.

Herring group	Total (n)	Stulberg classification (number of hips)				
		I	II	III	IV	V
A	7	2	1	2	2	0
B	40	12	20	3	4	1
B/C	12	0	8	1	2	1
C	15	1	6	2	5	1
Total (n)	74	15	35	8	13	3

Table 3. Correlation of risk factors on Stulberg outcome of 74 included patients.

	Correlations coefficient	95% CI	p-value
Herring group	0.32	0.03-0.61	0.03
Age at onset	0.20	0-0.40	0.05
Gender	0.38	-0.02-0.78	0.07
Lateral calcification	-0.08	-0.44-0.28	0.67
Metaphyseal cysts	0.29	-0.04-0.63	0.09
Horizontal growth plate	0.04	-0.29-0.20	0.73
Lateral subluxation	-0.13	-0.34-0.08	0.22
Gage's sign	-0.32	-0.71-0.07	0.11
Total number of head-at-risk signs	0.18	-0.10-0.45	0.21

Table 4. Intra-observer reliabilities of the modified Herring lateral pillar class, the head-at-risk signs, and Stulberg group expressed by weighted kappa coefficients.

	Weighted kappa coefficient
Herring class	0.89
Lateral calcification	0.42
Metaphyseal changes	0.90
Horizontal growth plate	0.85
Lateral subluxation	0.79
Gage sign	1.00
Stulberg group	0.93

11.2 The need for total hip arthroplasty in Perthes disease – a long term study

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Abstract

Background Legg-Calvé-Perthes disease (LCPD) was described a century ago. In previous long-term reports of patients with LCPD, nonoperative treatment varied considerably. The likelihood of hip osteoarthritis (OA) developing in patients with LCPD and possible need for THA are not well defined.

Questions/purposes The purpose of the study was to determine whether nonoperatively treated patients with LCPD (1) had an increased prevalence of THA compared with gender- and age-matched control subjects, (2) if patients with Stulberg Classes III/IV/V femoral heads had an increased risk of THA compared with those with Classes I/II femoral heads. Given the limitation in the study, we (3) evaluated whether patients with LCPD were at risk for having radiographic hip OA more commonly than control subjects and (4) whether hips with Classes III/IV/V femoral heads had an increased prevalence of OA compared with hips with Classes I/II femoral heads.

Patients and Methods The study population consisted of 167 patients with LCPD treated with a Thomas splint. The control population consisted of gender- and age-matched control subjects who were participants in the Copenhagen City Heart Study: the Osteoarthritis Substudy. Radiographs at skeletal maturity were classified according to the classification system of Stulberg et al. Data from the Danish Hip Arthroplasty Register and the Registries of the National Board of Health were collected to obtain the number of patients with LCPD having THA. At a mean followup of 47 years later (range, 37–58 years), weightbearing pelvic radiographs were obtained. Radiographic OA was defined as a joint space width of 2.0 mm or less.

Results Thirteen percent of patients with LCPD had THAs compared with none in the control group. Seven percent of the patients with LCPD had OA compared with 1% in the control group. The prevalence of THA and OA was increased in hips with Classes III/IV/V femoral heads compared with hips with Classes I/II femoral heads.

Conclusions Patients with LCPD have an increased risk of having THA compared with a gender- and age-matched control group. Our data suggest that patients with LCPD have a greater risk of having radiographic OA develop than a gender- and age-matched control group. It seems that patients with Classes III/IV/V femoral heads have an increased risk of THA and OA compared with patients with Classes I/II femoral heads.

Introduction

Numerous studies [2,5,6,10,12,14,15,16,18,20,21] have focused on the need for THA and long-term risk for having hip OA develop in nonoperatively treated patients with LCPD. Earlier studies are retrospective without any control group. In addition, the treatments have been combinations of several treatments such as: bed rest [6,12,14,15,16,18,20], traction [5,12,15], abduction splints [15,18], plaster [15], spica casting with [2,5,6,10,16,18] and without [2,5,6] weightbearing, Thomas splint [20,21], shoe elevation on the normal side [16,20], crutches [10,16,20], wheelchair [10], or no treatment [2,21]. In contrast, we evaluated one treatment method, namely, use of a Thomas splint. One major problem for the patients with LCPD in the long-term is development of hip pain and OA that might result in the need for a THA. Earlier studies have shown an overall prevalence of OA between 5% and 100% [2,5,6,10,12,14,16,20,21], and a prevalence of THA ranging from 0% to 24% [2,5,6,10,12,14-16,18,20,21] (Table 1).

Because of the wide variation reported in the literature, we determined whether nonoperatively treated patients with LCPD: (1) had an increased prevalence of THA compared with gender- and age-matched control subjects, and (2) if patients with Stulberg Classes III/IV/V femoral heads had an increased risk of THA compared with patients with Classes I/II femoral heads. Given the limitations of the study, we (3) evaluated whether patients with LCPD were at risk for having radiographic hip OA develop more commonly than control subjects, and (4) whether hips with Classes III/IV/V femoral heads had an increased prevalence of OA compared with hips with Classes I/II femoral heads.

Patients and Methods

This retrospective case-control study consists of a cohort of 167 patients (191 hips) with LCPD referred to The Community of Disabled in Kolding, Denmark from 1941 to 1962. One hundred forty-three patients had unilateral and 24 patients had bilateral involvement. All patients were treated by a Thomas splint regardless of gender, age at onset of the disease, and severity of disease. The Thomas splint is regarded as a noncontainment treatment and reportedly reduces load on the hip [11]. The splint was used from the time of diagnosis until the reconstitution stage of the disease appeared on the radiographs, a mean of 25 ± 9 months (range, 9–38 months). The splint was worn all day except when swimming and bathing. None of the patients had surgery during their childhood or were referred to other hospitals. The patient's gender, age at onset, and duration of treatment with a Thomas splint were obtained from the medical records. Onset of disease was defined as the

onset of limping or complaints of pain in the hip, thigh, or knee.

At skeletal maturity, supine AP and frog-leg lateral radiographs of the pelvis were taken. We defined skeletal maturity as the point when closure of the triradiate cartilage and the femoral head physis had occurred. One of the authors not involved in the treatment of the patients (LF) classified the radiographs according to the classification system of Stulberg et al. as reported by Herring et al.: Classes I and II hips have a spherical femoral head, a Class III hip has an ovoid head, and Classes IV and V hips have a flattened femoral head [3]. The advantages of the classification included the simplicity of application and reliability with interobserver and intraobserver agreement reflected by weighted kappa values of 0.79 and 0.88, respectively [3]. We combined Classes I and II as hips in these classes were considered not to be disposed to having OA develop and Classes III, IV, and V as these hips were considered to have an increased risk of having OA develop in adulthood, as reported in two studies [4,16].

Except for patients who were deceased, who had emigrated, or were lost to followup owing to lack of a civil registration number, all patients were invited to a followup in 2005–2006, and 111 accepted. For the 111 patients with LCPD, weightbearing standardized AP pelvic radiographs were obtained with a tube to film distance of 100 cm. Joint space width (JSW) was measured on AP pelvis radiographs (Fig. 1) by using a 0.1-mm graded magnifying glass (Haff, Pfronten, Germany). Hip OA was defined as a JSW of 2.0 mm or less regardless of the presence of osteophytes, subchondral sclerosis, or subchondral cysts [8]. One observer (LF) performed all measurements. We examined the data for 156 of the 191 hips to determine the risk for having a THA. Thirty-two patients (35 hips) were excluded: Five (six hips) owing to emigration, 23 (24 hips) were lost to followup, and four (five hips) had surgery before followup in pelvis or leg, not related to LCPD (Fig. 2). We were able to include deceased patients and patients who did not want to participate at followup in this part of the study, because data from the national Danish Hip Arthroplasty Register and the Registries of the National Board of Health were collected. Patients participating were asked whether they had a THA. In this part of the study, unilateral disease was present in 114 hips (73%) and bilateral disease in 42 hips (27%). There were 109 male patients (125 hips, 80%) and 26 female patients (31 hips, 20%) included in the study. Age at onset of disease was 6 ± 2 years and the Thomas splint was used for 25 ± 9 months. Of the 156 hips included, 57 (37%) were classified as having Classes I/II femoral heads, 26 (17%) had Classes III/IV/V femoral heads, and 73 (46%) were not classified owing to destroyed or missing radiographs. The classified hips did not differ regarding the patients' gender, age at onset, and duration of the Thomas splint compared

with hips that were not classified (Table 2).

To assess the prevalence of radiographic hip OA, 52 patients (54 hips) of the 167 patients (191 hips) were included. 115 patients (137 hips) were excluded owing emigration (five patients, six hips), lost to followup (23 patients, 24 hips), deceased (nine patients, 10 hips), refused to participate (19 patients, 21 hips), surgery in pelvis or lower limb before followup (19 patients, 26 hips), or missing or destroyed radiographs (40 patients, 50 hips) (Fig. 3). For this part of the study unilateral disease was present in 50 hips (93%) and bilateral disease in four (7%). There were 44 male patients (46 hips, 85%) and eight female patients (eight hips, 15%). Age at onset was 6 ± 2 years. The Thomas splint was used for 25 ± 7 months. Of 54 hips, 42 (78%) had Classes I/II femoral heads (Table 3). We observed no difference between hips with Classes I/II femoral heads and those with Classes III/IV/V femoral heads regarding gender, age at onset, and duration of time the Thomas splint was used (Table 3). Age at followup was 52 ± 4 years for males and 54 ± 5 years for females. Time from onset of disease until followup was 47 ± 5 years.

The prevalence of THA and radiographic OA was evaluated in a gender- and age-matched control group who were participants of The Copenhagen City Heart Study; Osteoarthritis Substudy [7]. The ratio of patients with LCPD to control subjects was 1:2. Radiographs for the control group were obtained with the patients standing and standardized with a tube to film distance of 120 cm. The difference between tube to film distances in the study and control groups was taken into consideration when measuring JSW.

Normality tests, by probit plots, showed all data were normally distributed. Thus, data are presented as means \pm standard deviation. The relationships between hip OA and THA in patients with LCPD and a gender- and age-matched control group were evaluated by exact logistic regression analysis. Odds ratio (OR) exact test was performed to assess interrelationship between class and THA and radiographic hip OA. The T-test was used to evaluate differences between demographic data. All statistical analyses were performed with the STATA[®] Version 10.0 statistical software (StataCorp LP, College Station, TX, USA).

Results

The risk of THA was increased from none of 312 hips (0%) in the gender- and age-matched control group compared with 20 of 156 hips (13%) in the patients with LCPD ($p < 0.001$; OR = 49.0; CI = 8.2–infinity) (Table 4). None of the patients who emigrated had a THA performed in Denmark.

Whether they had a THA performed outside Denmark is unknown.

The risk of THA was increased from five of 57 hips (9%) with Classes I/II femoral heads to seven of 26 hips (27%) with Classes III/IV/V femoral heads ($p = 0.04$; OR = 3.8; CI = 1.1–12.9) (Table 4).

The risk of radiographic OA was increased from one of 108 hips (1%) in the gender- and age-matched control group to four of 54 hips (7%) in the patients with LCPD ($p = 0.04$; OR = 8.5; confidence interval [CI] = 1.8–428.8) (Table 5).

The risk of radiographic OA was increased from one of 42 hips (2%) with Classes I/II femoral heads compared with three of 12 hips with Classes III/ IV/V femoral heads ($p = 0.03$; OR = 13.7; CI = 1.9–97.1) (Table 5).

Discussion

The long-term problems for patients with LCPD are the risk for having hip pain and OA develop and the subsequent need for a THA. In previous reports [2,5,6,10,12,14,15,16,18,20,21], treatment of the patients and definition of OA varied considerably (Table 1), and the prevalence of THA and OA in a gender- and age-matched population have not been taken into account. The current case-control study determined whether nonoperatively treated patients with LCPD (1) had an increased prevalence of THA compared with gender- and age-matched control subjects, and (2) if patients with Stulberg Classes III/IV/V femoral heads had an increased risk of THA compared with patients with Classes I/II femoral heads. Given the limitations of the study, we evaluated (3) whether patients with LCPD have radiographic hip OA develop more commonly than control subjects, and (4) whether hips with Classes III/IV/V femoral heads had an increased prevalence of OA compared with hips with Classes I/II femoral heads.

There are limitations to our study. First, the study is based on AP radiographic findings, and the clinical status of the patients was not evaluated. We used only AP radiographic findings as a lateral view was not obtained for the control subjects. Second, our study comprises a small number of patients. Owing to different inclusion criteria, 156 of 191 hips (82%) were included in the THA study (Fig. 2) and 54 of 191 hips (28%) were included in the OA study (Fig. 3). Third, owing to inadequate or destroyed radiographs, it was possible to classify only 83 of the 156 (53%) hips in the THA study. Third, OA was defined as JSW narrowing regardless of the presence of osteophytes, sclerosis, and cysts. One study showed a substantial association between a reduced JSW and self-reported hip pain [9]. We used a reduced JSW of 2.0 mm or less as a specific definition of radiographic OA as it has been associated with self-reported hip pain and has an acceptable

intrarater reliability (intraclass correlation coefficients, 0.87-0.91) [9]. This is in contrast to Dieppe et al. [1], who found no correlation between pain, stiffness and physical function, and radiographic severity evaluated by the Kellgren and Lawrence radiographic score. This might be explained by differences in clinical and radiographic evaluations of the patients. Sun et al. [17] found that interrater reliability of JSW narrowing showed a high reliability compared with other radiographic features of OA (Kappa, 0.70-0.79). In contrast, the interrater reliability of the Kellgren and Lawrence score has a lower kappa value (0.50). Fourth, although we expended much effort trying to find the patients and obtain radiographs, some patients had emigrated, some were deceased, and others did not want to participate or were lost to followup owing to lack of a civil registration number; other patients were located but did not keep followup appointments. The current study is comprised of patients with a followup of nearly 50 years. We were able to trace 144 patients (167 of 191 hips, 87%) registered in our archives who were diagnosed with LCPD from 1941 to 1962, and in contrast to other studies [2,5,6,10,12,14,15,16,18,20,21], all children had the same weight-relieving noncontainment treatment in their childhood regardless of gender, age at onset, degree of femoral head involvement, and unilateral or bilateral involvement. We were able to include 156 of 191 (82%) hips in the THA study, since the patients could be found in the Danish Hip Arthroplasty Register and The Register of the National Board of Health. In the OA study 54 of 191 hips (28%) were included; therefore, the risk of misinterpretation of the results in this part of the study should be taken into account.

We do not believe any patients were missed at followup in this part of the study owing to insufficient or incorrect registration. The Danish Hip Arthroplasty Register has existed since 1995 and has a 94.1% complete rate for registration for primary THA [13]. In The Register of the National Board of Health, every operation performed in Denmark has been recorded under a unique personal civil registration number since 1977 [19]. The civil registration number is used in every contact with the public system in Denmark and follows each individual his/her entire life and after death. Fifth, it was possible to classify only 83 of the 156 (53%) hips in the THA study. However, we have no reason to believe that hips with and without a classification were biased as no difference was found regarding gender, age at onset, and duration of use of the Thomas splint. For assessment of radiographic OA, 137 of 191 hips (72%) were excluded. However, except for patients excluded owing to surgery before followup (19 patients, 26 hips), we have no reason to believe that the excluded and included patients differed. Of the surgically treated hips, 20 had LCPD-related THA. Finally, no preoperative radiographs were available for 17 hips, and in three hips with preoperative

radiographs, the JSW observed on AP radiographs of the pelvis was greater than 2.0 mm, and according to our definition, without OA. In the OA study, 42 of 54 hips (78%) were classified as having Classes I/II femoral heads, which is a high percentage compared with the study of Herring et al. [4]. This difference might be attributable to patients in our study who were excluded owing to THA; these patients were more likely to have Classes III/IV/V femoral heads, as shown in the Results section.

The prevalence of THA was 13% in patients in the current study compared with 0% to 24% reported in previous studies [2,5,12,14,20]. The studies have mean followups ranging from 28 to 50 years, which might explain the difference (Table 1). For 83 of 156 hips (53%) with a Stulberg et al. [16] classification, the risk of having THA was increased threefold for hips with Classes III/IV/V femoral heads compared with hips with Classes I/II femoral heads, which is in accordance with the increased risk of radiographic OA resulting from the disease [6,16].

The overall prevalence of OA for patients in the current study was 7%. This is lower compared with some other studies [2,5,6,12,15,16,20,21], and might be attributable to the difference in the definition of OA (Table 1). Perpich et al. [14] defined OA as a JSW narrowing less than 2.0 mm compared with the other hip. The prevalence of OA in their patients was 8% which is in concordance with our results.

Given the limitations, our data suggest that patients with Classes III/IV/V femoral heads were more likely to have radiographic OA develop than patients with Classes I/II femoral heads. The prevalence of OA in patients in the current study was 2% for those with Classes I/II femoral heads and 25% for those with Classes III/IV/V femoral heads. In contrast, Stulberg et al. [16] reported that 3% of patients with Classes I/II femoral heads and 63% of patients with Classes III/IV/V femoral heads had radiographic signs of OA develop 40 years after onset of disease (Table 1). In the study by Ippolito et al. [6], the prevalence of OA after 25 years was 0% for patients with Classes I/II femoral heads and 47% for those with Classes III/IV/V femoral heads (Table 1). In both studies, OA was defined as either narrowing of the JSW, presence of osteophytes, subchondral sclerosis, or subchondral cysts, which might explain the differences between those studies [6,16] and our study. Patients with LCPD have an increased risk of having THA compared with a gender- and age-matched control group. Our data suggest that patients with LCPD have a greater risk of having radiographic OA develop than a gender- and age-matched control group. It seems that patients with Classes III/IV/V femoral heads have an increased risk of THA and OA compared with patients with Classes I/II femoral heads.

Acknowledgments

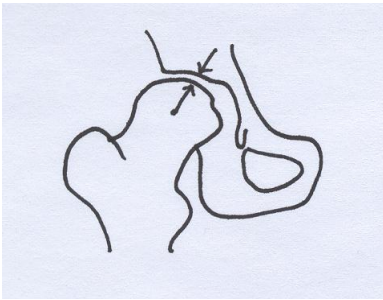
We thank Stig Sonne-Holm MD, PhD, and Steffen Jacobsen MD, PhD, from the Department of Orthopaedic Surgery, Copenhagen University Hospital, Hvidovre Hospital, Copenhagen, for permission to study radiographs of patients from The Copenhagen City Heart Study; Osteoarthritis Substudy. Lars Korsholm PhD, Institute of Public Health, was helpful with the statistical work.

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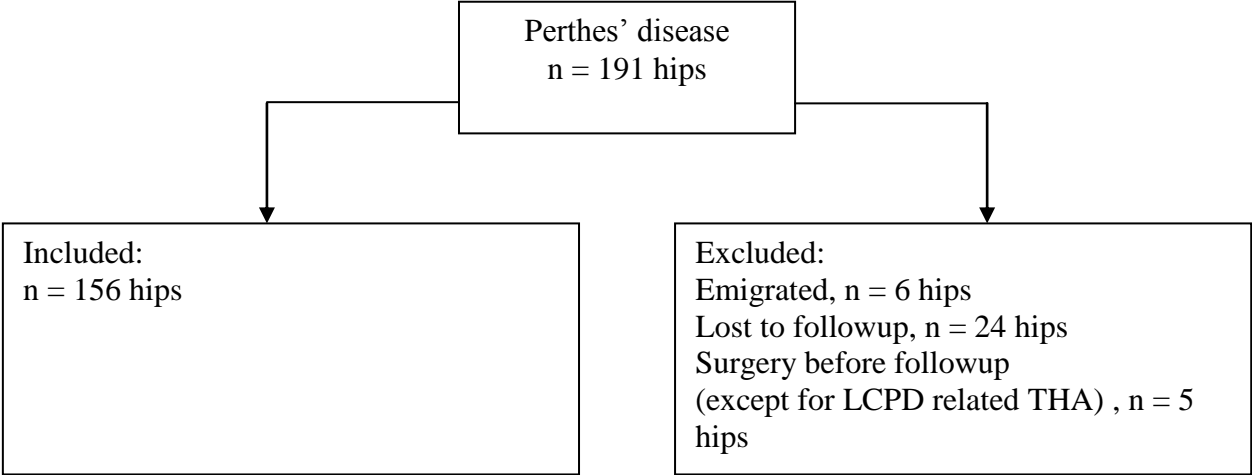
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Figur 1. Measurement of minimal JSW was performed perpendicular to the femoral head surface by determining the femoral head center using a best-fit circle and drawing lines from the center to the acetabular weightbearing surface. The JSW from the femoral head surface to the acetabulum was measured at three sites chosen where the smallest distance visual was present and not on predefined locations, as the caput and acetabulum in some patients were incongruent. The JSW used for statistical analysis was the smallest of the measurements.



Figur 2. A flowchart shows the patients eligible for evaluation of THA.



Figur 3. A flowchart shows the patients eligible for evaluation of hip OA.

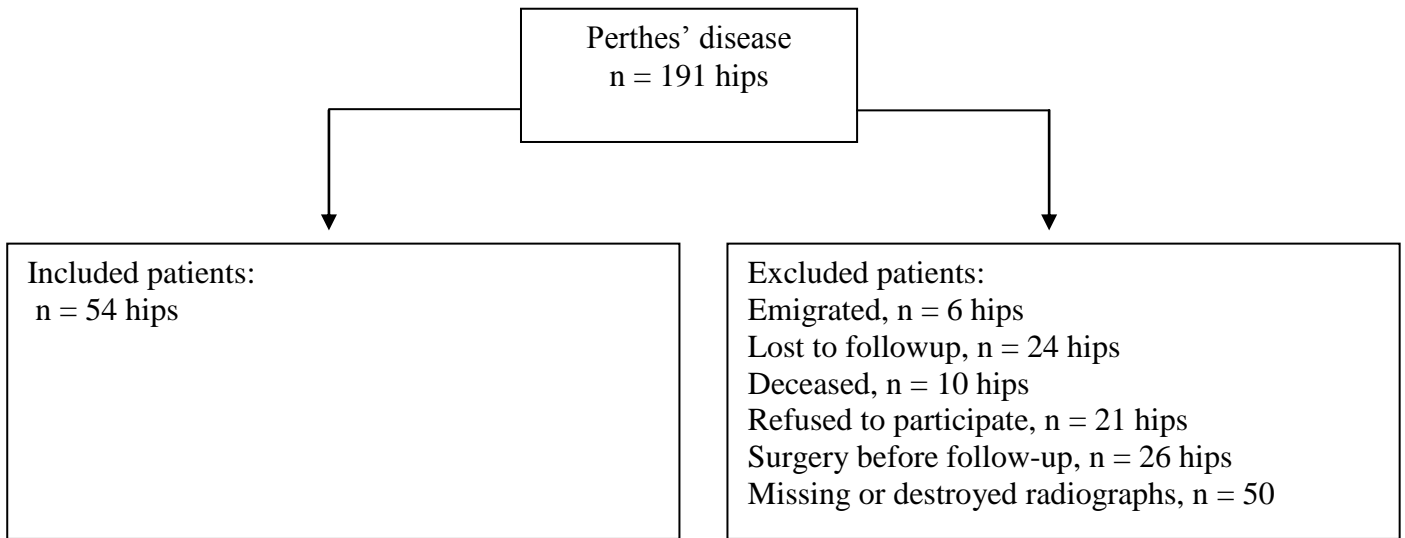


Table 1. Previous articles on conservatively treated LCPD patients.

Author	Followup /years	Prevalence of THA	Definition of radiographic OA	Prevalence of OA
Gower WE et al [2]	36	3/36 hips (8%)	Not specified	23/30 (77%)
Ippolito E et al [5]	27	1/11 (9%)	Sclerosis, JSW narrowing, osteophytes	10/10 (100%)
Ippolito E et al [6]	25	0/61 (0%)	Sclerosis, JSW narrowing, osteophytes, cysts	Stulberg I:0/8 (0%) Stulberg II:0/17 (0%) Stulberg III:9/25 (37%) Stulberg IV:7/10 (70%) Stulberg V:1/1 (100%)
Kelly FB et al [10]	22	2/80 (3%)	Not specified	4/80 (5%)
Lecuire F [12]	50	12/51 hips (24%)	Not specified	7/32 hips (22%)
Perpich M et al [14]	29	3/38 (8%)	JSW less than 2mm compared to the other hip	3/41 hips (7%)
Rush J [15]	26	0/35 (0%)	Not specified	Not specified
Stulberg D et al [16]	40	0/171 (0%)	Sclerosis, JSW narrowing, osteophytes, cysts	Stulberg I:0/20 (0%) Stulberg II:2/30 (7%) Stulberg III:10/28 (36%) Stulberg IV:28/42 (67%) Stulberg V:26/32 (81%)
Templeton J et al [18]	32	0/37 (0%)	Not specified	Not specified
Yrjönen T et al [20]	35	0/19 (0%)	Not specified	12/19 hips (63%)
Yrjönen T [21]	35	5/106 (5%)	Sclerosis, JSW narrowing, osteophytes, cysts	51/106 (48%)

Table 2. Demographic data of hips with and without a Stulberg classification in the THA study.

	Stulberg class I/II n = 57 hips	Stulberg class III/IV/V n = 26 hips	Without Stulberg classification n = 73 hips	p-value for difference between patients classified and not classified
Ratio male:female	4:1	3:1	4:1	0.42
Age at onset/years	6 ± 2	6 ± 3	6 ± 2	0.21
Duration of Thomas splint/months	25 ± 6	25 ± 9	25 ± 12	0.89

Table 3. Demographic data of hips in Stulberg class I/II and Stulberg class III/IV/V in the OA study.

	Stulberg Class I/II n = 42 hips	Stulberg Class III/IV/V n = 12 hips	p-value
Ratio male:female	7:1	3:1	0.40
Age at onset/years	6 ± 2	6 ± 2	0.75
Duration of Thomas splint/months	25 ± 7	24 ± 6	0.77

Table 4. Number of hips having a THA in LCPD patients and a gender- and age-matched control group.

	THA	No THA
LCPD group		
Stulberg class I/II (n = 57)	5 (9%)	52 (91%)
Stulberg class III/IV/V (n = 26)	7 (27%)	19 (73%)
Unknown Stulberg class (n = 73)	8 (11%)	65 (89%)
Sex- and age-matched control group (n = 312)	0 (0%)	312 (100%)

Table 5. Number of hips with or without hip OA in the LCPD group and a gender- and age-matched control group

Group	Number of hips with OA	Number of hips without OA
LCPD group		
Stulberg Class I/II (n = 42)	1 (2%)	41 (98%)
Stulberg Class III/IV/V (n = 12)	3 (25%)	9 (75%)
Control group (n = 108)	1 (1%)	107 (99%)

OA was present when the joint space width was 2.0 mm or less regardless of other features of OA; OA = osteoarthritis; LCPD = Legg-Calvé-Perthes disease.

11.3 Radiographic changes in the hip joint in children suffering from Perthes disease. A case control study

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Abstract

Objective: The purpose was to compare radiographic parameters with a sex- and age-matched control group at onset of disease and at skeletal maturity.

Methods: The study consisted of 143 patients with Legg-Calvé-Perthes disease treated by a Thomas splint. Wiberg's center-edge angle and the acetabular index angle were applied.

Results: At the time of diagnosis, the center-edge angle was decreased from 18 degrees in the control group to 10 degrees on the affected hip. At the time of skeletal maturity, the center-edge angle was decreased and the acetabular index angle increased in the affected hip and the non-affected hip in Stulberg class III/IV/V hips compared with the control group.

Conclusions: Initially radiographic changes only occur on the affected hip. At skeletal maturity both hips have radiographic changes.

Introduction

It is well known that growth of the proximal femur and acetabulum are interdependent and that containment is of great importance to achieve a congruent joint without deformities in the normal hip joint [1,2].

The majority of previous Legg-Calvé-Perthe disease (LCPD) studies have focused on femoral head and neck changes in the affected hip. Fewer studies have examined the morphological changes in the ipsilateral acetabulum [2-9] and in the non-affected hip [10-13].

Most studies on the changes in the hip joint in LCPD patients assume that the acetabular changes are secondary to those in the femoral head [2,3,6-9]. However; another study reports evidence that some of the acetabular changes develop early in the course of the disease and do not necessarily follow the alterations in the shape of the femoral head [5]. In contrast, another found the shape of the acetabulum important during the remodelling of the deformed head [4].

The purpose of the study was firstly, to compare radiographic parameters used for dysplasia in LCPD patients with a control group, and secondly, to evaluate whether the radiographic changes in the hip joint were present at the time of diagnosis or whether they developed later.

Methods

Study group

Between 1941 and 1962, 143 patients with unilateral LCPD presented at The Community of Disabled in Kolding, Denmark. All patients were treated conservatively with a Thomas splint

regardless of severity of disease, gender and age at onset of disease. Since the Thomas splint only partly reduces weight on the hip joint [14], the results of this study were considered to follow a course identical to, or close to the natural history of the disease [15]. The Thomas splint was used from the time of diagnosis until the reconstitution stage of the disease appeared on the radiographs. If leg length discrepancy was present when the Thomas splint was applied, the sole of the shoe was raised on the side of the non-affected hip. None of the patients had surgery in their childhood and to our knowledge none of the patients were referred to other hospitals. The medical records of the patients were retrieved retrospectively and gender, age at onset, and duration of treatment with the Thomas splint were registered.

At the fragmentation stage of the disease antero-posterior (AP) radiographs of the pelvis were classified according to the modified Herring lateral pillar classification [16]. The patient's radiographs from the time of diagnosis were then obtained and the radiographic dysplastic parameters measured. The time of diagnosis of disease was defined when necrosis or collapse of the femoral head in either AP or frog-leg lateral radiographs appeared for the first time. We combined Herring group A and B hips since they were expected to end in Stulberg class I and II, and combined Herring group B/C and C hips which were expected to end in Stulberg class III, IV or V [17].

At skeletal maturity supine AP and frog-leg lateral radiographs of the pelvis and the hips were classified according to the revised Stulberg's classification system, where class I and II hips have a spherical femoral head, class III hips an ovoid head and class IV and V hips a flat femoral head [16]. We combined Stulberg class I and II since they were considered not to be at risk of developing osteoarthritis, and class III, IV and V since they were considered to have an increased risk of developing osteoarthritis in adulthood [11,17,18]. Skeletal maturity was defined as closure of the triradiate cartilage and the femoral head physis. Patients with missing or destroyed radiographs were excluded. Thus, 74 patients were included (Fig. 1).

Control group

To compare the measurements in LCPD patients with a background population, age- and sex-matched control persons were obtained from our institutions. It was not considered ethical to ask for radiographs of normal children, therefore a control group was obtained from sex- and age-matched children who had had radiographs made of their pelvis due to a trauma (n=104) or due to transient synovitis of the hip joint (n=44). The radiographs had to be described without reference to LCPD,

osteomyelitis, fracture, epiphysiolysis, tumour or arthritis by a senior radiologist. The control persons were excluded if they had radiographic signs of one of these findings within three months after they had transient synovitis. The ratio of LCPD patients to control persons was 1:1.

Radiographic parameters for hip dysplasia

We measured Wiberg's centre-edge angle (CE angle) (Fig. 2) and the acetabular index angle (AA angle) (Fig. 3) in AP radiographs of the pelvis at the time of diagnosis of the disease and at skeletal maturity.

Statistics

A normality test, using probit plots, showed that all data were normally distributed. Thus data are presented as mean and standard deviation (s.d).

Linear regression analysis by means of STATA cluster option was used to evaluate if LCPD patients had significantly different mean radiographic values compared with the control group.

All statistical analyses were performed with the STATA[®] version 10.0 statistical software (StataCorp LP, College Station, TX). A p-value less than 0.05 was considered statistical significant.

Results

Seventy-four patients (61 boys) were included in this study. The right side was affected in 35 (47%) of the patients. Age at diagnosis was 6.6 (s.d 2.1) years and there was no significant difference in the age between boys (6.5 years, s.d 1.8) and girls (7.0 years, s.d 2.9). Age at skeletal maturity was 16 (s.d 2) years for the boys and 15 (s.d 3) years for the girls. The Thomas splint was used for 29 (s.d 5) months. Forty-seven out of 74 patients (64%) were classified as Herring group A and B, and 27 out of 74 patients (36%) were classified as Stulberg class I/II.

Time of diagnosis

The CE angle at the time of diagnosis of the disease was significantly decreased in the affected hip from 18 degrees in the control group to 10 degrees in Herring group A and B ($p < 0.0001$ [95% CI 8-12]) (Table 1a), and also decreased the same amount in Herring group B/C and C ($p < 0.0001$ [95% CI 4-12]) (Table 1c). The AA angle in the affected hip did not differ from the control group (Table 1a and 1c) (Figure 4).

In the non-affected hip, the CE angle and the AA angle did not differ from the control group (Table 1b and 1d).

Time of skeletal maturity

In the affected hip at the time of skeletal maturity, the CE angle was significantly decreased and the AA angle significantly increased compared with the control group regardless of Stulberg classes (Table 2a and 2c).

In the non-affected hip the CE angle and AA angle in Stulberg class I/II did not differ from the control group (Table 2b). However; in the non-affected hip in Stulberg class III/IV/V the CE angle was significantly decreased from 26 degrees to 14 degrees ($p=0.001$ [95%CI 8-20]), and the AA angle significantly increased from four degrees in the control group to 12 degrees ($p=0.010$ [95%CI 8-16]) compared with the control group (Table 2d) (Figure 5).

Discussion

LCPD has been known for a century, yet the cause of the disease and changes in the hip joint are not fully understood. We evaluated the radiographic changes in LCPD patients using the CE angle and AA angle at the time of diagnosis of the disease and at skeletal maturity. To our knowledge, no case-control studies exist describing the radiographic morphology of either the affected hip or the contralateral hip in children suffering from LCPD.

The strengths of our study were firstly that the same conservative treatment regime with a Thomas splint was applied to all the children regardless of gender, age at onset, and degree of femoral head involvement. The Thomas splint does not fix the hip in a contained position, but it does reduce weight on the hip joint [14]. We considered the results following this treatment identical or close to the natural history of the disease [15]. Secondly, a sex- and age-matched control group was obtained in order to adjust for abnormal radiographic measurements in the control group. Thirdly, the measures for hip dysplasia were made at the time of diagnosis when no secondary changes in the femoral head and acetabulum were expected. Finally, the revised Stulberg classification was used as well as radiographic parameters with high inter- and intra-observer reliability [16,19].

Our study has limitations due to the small number of patients. However, the ratio of boys to girls included in this study was 4.7:1 and the mean age at diagnosis was 6.6 years, which is similar to other studies [20,21,22]. The severity of disease in the current study was similar to the study by

Herring *et al.* [17]. Thus it seems that the patients included in this study were neither biased according to gender, age at diagnosis, nor severity of the disease.

For the control group, we used radiographs of children suffering from trauma or transient synovitis. Some of the children with transient synovitis had an increased amount of fluid in the hip joint evaluated by ultrasound. This might have lateralised the femoral head and thereby decreased the CE angle. However, there was no difference in CE angle and AA angle in the hips suffering from transient synovitis and the contralateral hip of those children. Moreover, no significant difference was present between the radiographic measurements in patients suffering from transient synovitis and trauma. Hence, we have no reason to believe that the CE angle in the control group was biased. In the current study the CE angle in the affected hip at the time of diagnosis of LCPD was significantly decreased to 10 degrees regardless of Herring group compared to 18-19 degrees in the non-affected hip and in hips from the control group. In contrast the AA angle in the affected hip was normal compared with the control group. According to Tönnis [23] the lowest normal CE angle value for children at the age five to eight years is 19 degrees. This suggests that the acetabulum is normal at the onset of disease and that the femoral head is lateralised due to synovitis or widening of the femoral head due to cartilaginous hypertrophy. At skeletal maturity the CE angle was significantly decreased in both Stulberg class I/II and Stulberg class III/IV/V. This could be explained by the presence of coxa magna or the presence of a deformed femoral head. In the presence of coxa magna, the radius enlarges and the centre of the femoral head moves laterally, which decreases the CE angle. However, no difference between the CE angle in the spherical femoral head in Stulberg class I hips (without coxa magna) and Stulberg class II hips (with coxa magna) was found ($p=0.5$) suggesting that the decreased CE angle is not a result of coxa magna. The AA angle at skeletal maturity was significantly increased in the affected hips regardless of Stulberg class. This suggests that the acetabulum moulds partly to the femoral head during the healing process. This issue is supported by previous reports [2,3,6,7,8,9] where changes of the femoral head occurred first and changes in the acetabulum followed.

Surprisingly, at skeletal maturity the CE angle and AA angle in the non-affected hip in Stulberg class III/IV/V were significantly different from those in the control group (table 3d). This, to our knowledge, has not been shown before. Arie *et al.* [10] found that the non-affected hips in children with LCPD show anterior and lateral flattening of the femoral head, indicating that the non-affected hip can also become affected during the active phase of the disease. Murphy *et al.* [13] suggest that the radiographic changes might be explained by the affected leg being shorter than the non-affected,

causing increased adduction of the femoral head and as a consequence, less acetabular coverage. Our results suggest that the non-affected hip in severe cases might be influenced by the contralateral hip.

In conclusion, this study demonstrates that in the affected hip of LCPD patients the femoral head changes initially occur in a normal acetabulum, which secondarily becomes deformed. In the non-affected hip the radiographic measurements were normal at the time of diagnosis of the disease, but were significantly different in Stulberg class III/IV/V compared with the control group when the child reached skeletal maturity.

Acknowledgements

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Figure 1. Diagram of patients with Perthes' disease in this retrospective study (n=number of patients).

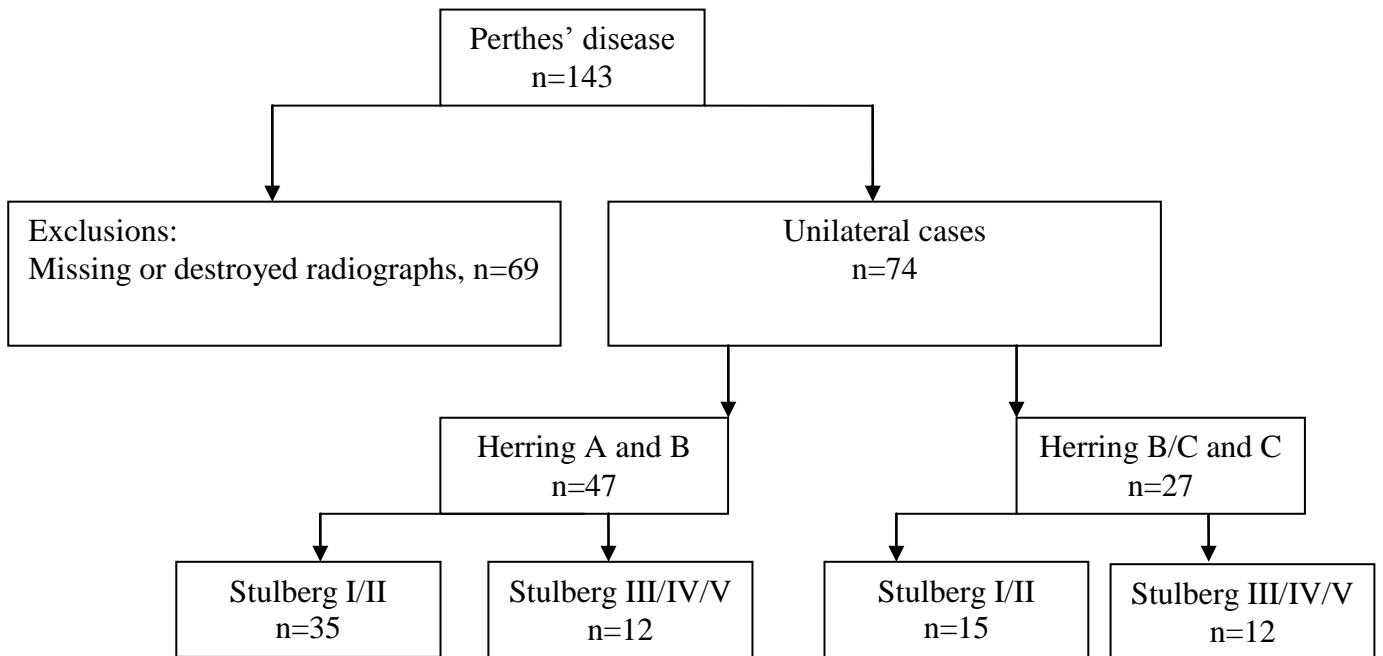


Figure 2. The CE angle of Wiberg designates the angle between a line perpendicular to a horizontal line through the femoral head centre (a) and a line from the femoral head centre to the lateral edge of the acetabular weight-bearing surface (b). The horizontal line was drawn through tear drop.

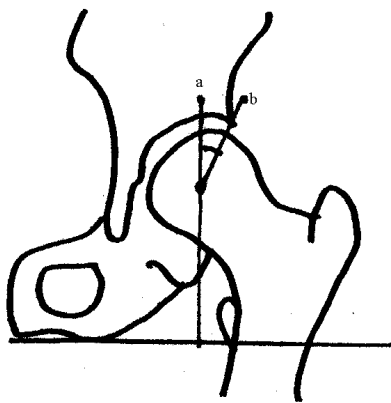


Figure 3. The acetabular index angle is measured as the angle between a line from the lateral edge of the acetabular weight-bearing surface to the medial sclerotic line of the acetabulum (a) and a horizontal line parallel to a line at the lower point of tuber ischii (b).

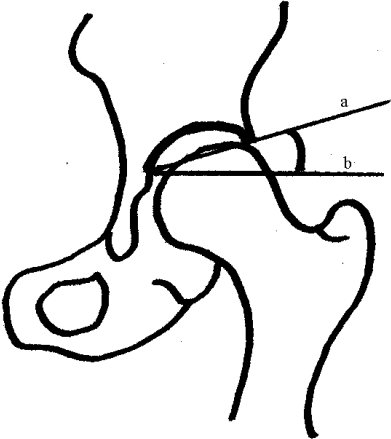


Figure 4. 4 years and 1 month old boy with affected right hip. At the non-affected left hip were the CE angle 10 degrees and the AA angle 15 degrees. The CE angle on the affected left hip was -11 degrees and the AA angle was 16 degrees.

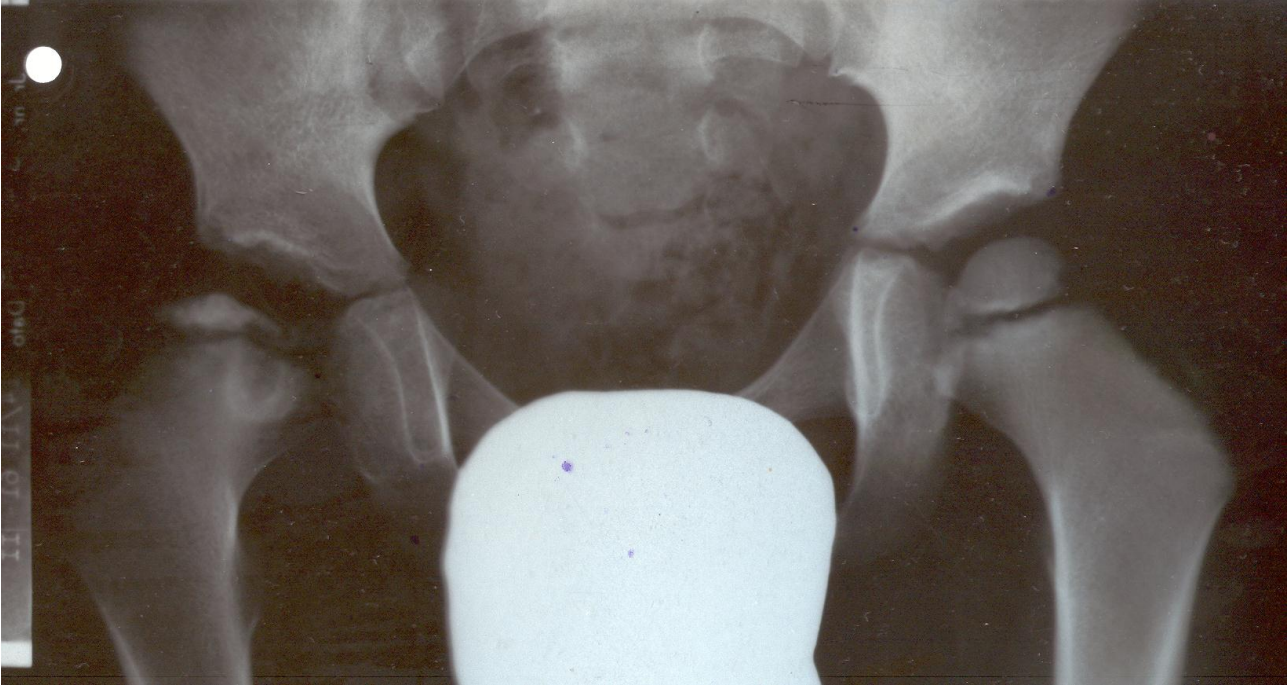


Figure 5. 18 years old boy with left Stulberg class IV hip. At the non-affected right hip were the CE angle 23 degrees and the AA angle 13 degrees. The CE angle on the affected left hip was 18 degrees and the AA angle was 6 degrees. Hence both of the hips were dysplastic.

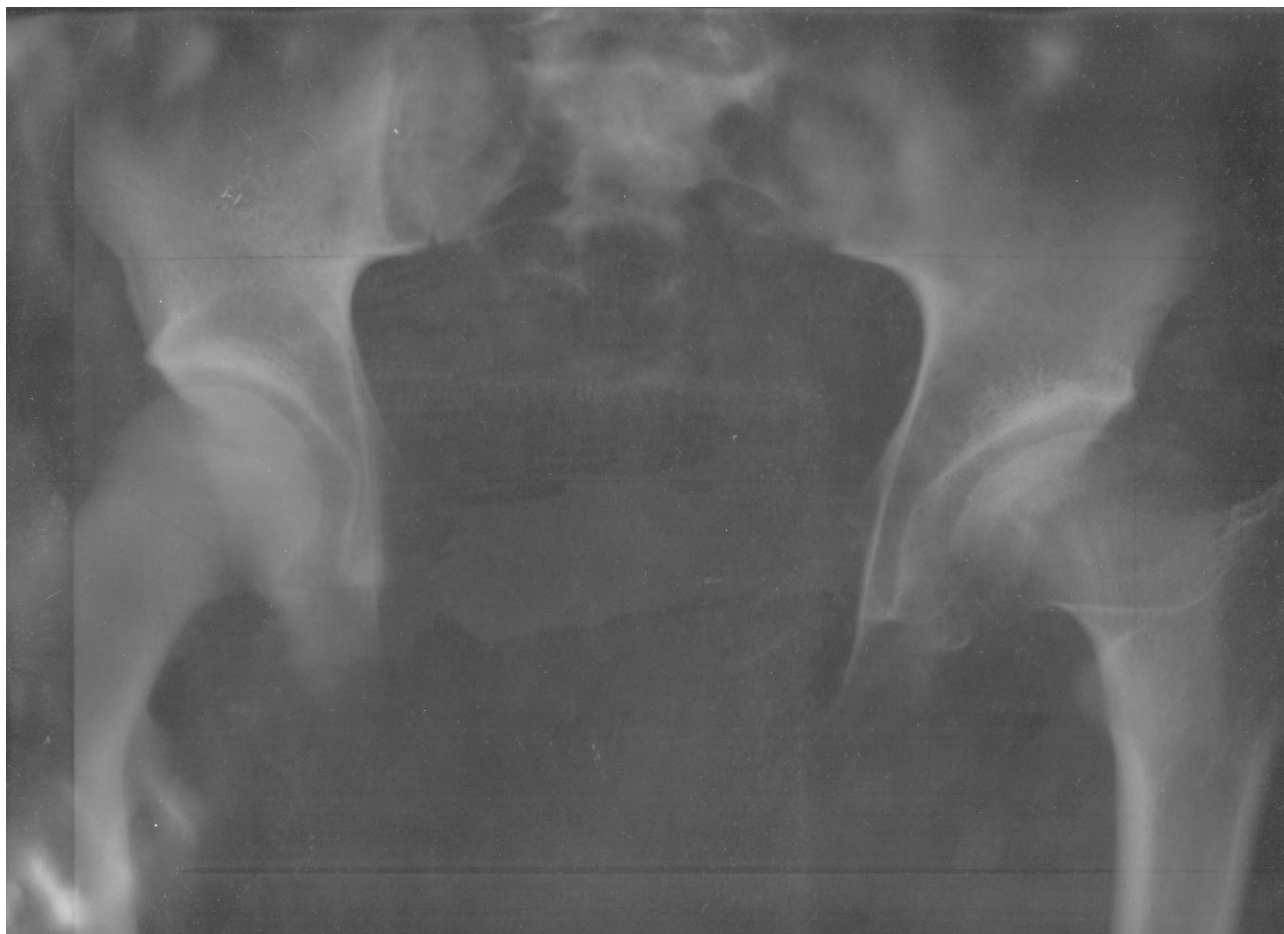


Table 1. The CE angle and AA angle at diagnosis of LCPD patients divided into Herring group and affected and non-affected hips. Patients with LCPD are compared with a sex- and age-matched control group. The mean values, standard deviation (s.d) and 95% confidence intervals (95%CI) are shown.

1a. Radiographic measurements at diagnosis of disease Affected hip, Herring group A and B				1b. Radiographic measurements at diagnosis of disease Non-affected hip, Herring group A and B			
	Perthes disease n=47	Control n=47	p-value		Perthes disease n=47	Control n=47	p-value
CE angle	10 s.d 7 95%CI 8-12	18 s.d. 6 95%CI 16-20	<0.0001	CE angle	19 s.d 6 95%CI 17-20	18 s.d. 5 95%CI 16-19	0.463
AA angle	10 s.d 4 95%CI 9-12	9 s.d. 4 95%CI 8-10	0.173	AA angle	9 s.d 5 95%CI 8-10	10 s.d. 5 95%CI 9-12	0.220
1c. Radiographic measurements at diagnosis of disease Affected hip, Herring group B/C and C				1d. Radiographic measurements at diagnosis of disease Non-affected hip, Herring group B/C and C			
	Perthes disease n=27	Control n=27	p-value		Perthes disease n=27	Control n=27	p-value
CE angle	10 s.d 8 95%CI 4-12	18 s.d. 7 95%CI 15-21	<0.0001	CE angle	19 s.d 8 95%CI 13-23	19 s.d. 7 95%CI 17-22	0.753
AA angle	10 s.d 7 95%CI 5-13	11 s.d. 6 95%CI 9-14	0.399	AA angle	9 s.d 5 95%CI 6-13	9 s.d. 5 95%CI 7-11	0.812

Table 2. The CE angle and AA angle at skeletal maturity of LCPD patients divided into Stulberg class and affected and non-affected hips. Patients with LCPD are compared with a sex- and age-matched control group. The mean values, standard deviation (s.d) and 95% confidence intervals (95%CI) are shown.

2a. Radiographic measurements at skeletal maturity Affected hip, Stulberg class I/II				2b. Radiographic measurements at skeletal maturity Non-affected hip, Stulberg class I/II			
	Perthes disease n=51	Control n=51	p-value		Perthes disease n=51	Control n=51	p-value
CE angle	24 s.d 8 95%CI 22-26	29 s.d. 5 95%CI 28-30	<0.0001	CE angle	25 s.d 9 95%CI 23-27	27 s.d. 6 95%CI 25-29	0.104
AA angle	7 s.d 7 95%CI 5-9	3 s.d. 6 95%CI 1-5	0.029	AA angle	6 s.d 5 95%CI 5-7	4 s.d. 5 95%CI 3-5	0.170
2c. Radiographic measurements at skeletal maturity Affected hip, Stulberg class III/IV/V				2d. Radiographic measurements at skeletal maturity Non-affected hip, Stulberg class III/IV/V			
	Perthes disease n=23	Control n=23	p-value		Perthes disease n=23	Control n=23	p-value
CE angle	15 s.d 15 95%CI 9-21	28 s.d. 5 95%CI 26-30	<0.0001	CE angle	14 s.d 14 95%CI 8-20	26 s.d. 5 95%CI 24-28	0.001
AA angle	11 s.d 9 95%CI 7-13	3 s.d. 6 95%CI 1-5	0.003	AA angle	12 s.d 11 95%CI 8-16	4 s.d. 6 95%CI 2-6	0.010

11.4 Prevalence of hip dysplasia in Legg-Calvé-Perthes disease. A case-control study

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Submitted

Abstract

Background. Previous studies have described the risk of hip osteoarthritis and total hip replacement in Legg-Calvé-Perthes disease (LCPD) patients, while the prevalence of hip dysplasia, to our knowledge, has not been described.

Purposes. The purposes of this study were to determine whether LCPD patients (1) had an increased prevalence of hip dysplasia and (2) to compare the absolute values of Wiberg's centre-edge angle (CE angle), the acetabular index angle (AA angle) and femoral head extrusion index (FHEI) in both the affected and non-affected hip with a control group.

Methods. The study population consisted of 143 conservatively treated LCPD patients. Radiographs at skeletal maturity were classified according to the Stulberg classification system. At follow-up, on average 47 years later, antero-posterior radiographs were obtained. The radiographic parameters were measured. The control group consisted of age- and gender-matched persons obtained from the Copenhagen City Heart Study; the Osteoarthritis Substudy.

Results. In the affected hip minimum 38 percent of the LCPD patients had hip dysplasia compared with maximum 16 percent in the control group ($p < 0.05$). Overall in the affected hip the CE angle and FHEI were decreased and the AA angle increased regardless of Stulberg Class. In the non-affected hip in Class III/IV/V the CE angle was decreased in the LCPD patients ($p < 0.01$) and the AA angle increased ($p = 0.01$).

Conclusions. LCPD patients have a significantly increased prevalence of hip dysplasia in the affected hip regardless of Stulberg Class. The non-affected hip in Class III/IV/V can also have radiographic changes.

Introduction

Legg-Calvé-Perthes disease (LCPD) has been known for a century, yet the cause of the disease and the associated changes in the hip joint are not fully understood. Long-term studies often report the prevalence of osteoarthritis and the need for total hip replacement [4,10,11,15,18], but to our knowledge no previous report has described the prevalence of hip dysplasia in adult LCPD patients. Furthermore; only few studies have described dysplastic changes in the hip joint in patients previously suffering from LCPD [2,12,14].

The purposes of this study were (1) to determine whether nonoperatively treated patients with LCPD had an increased prevalence of hip dysplasia in the affected and non-affected hip, compared with a control group and (2) to compare the absolute values of Wiberg's centre-edge angle (CE

angle), the acetabular index angle (AA angle) and femoral head extrusion index (FHEI) in LCPD patients and a control group.

Patients and Methods

Study group

From 1941 to 1962, 143 patients with unilateral LCPD presented at The Community of Disabled in Kolding, Denmark. All patients were treated conservatively with a Thomas splint regardless of severity of disease, gender and age at onset of disease. The splint was used from the time of diagnosis until the reconstitution stage of the disease appeared on the radiographs. The child wore the splint all day except when swimming or bathing. None of the patients had surgical treatment in their childhood and to our knowledge none of the patients were referred to other hospitals.

Retrospectively, the patient's gender, age at onset and duration of treatment with a Thomas splint were obtained from the medical records. Onset of disease was defined as the onset of limping or complaining about pain in the hip, thigh or knee.

At skeletal maturity supine antero-posterior (AP) and frog-leg lateral radiographs of the pelvis and the hips were classified according to the revised Stulberg's classification system. We combined Class I and II hips since they had spherical femoral heads, and Class III, IV and V hips which have ovoid or flat femoral heads [5]. Skeletal maturity was defined as closure of the triradiate cartilage and the femoral head physis.

Fifty-one of the original patients had either emigrated ($n = 4$), become diseased ($n = 8$), were lost to follow-up ($n = 22$) or refused to participate ($n = 17$). The remaining patients were invited to a radiographic examination in 2005-06. Weight-bearing standardized AP pelvic radiographs were obtained with a tube to film distance of 100 cm. The following exclusion criteria were applied: 1) Insertion of total hip arthroplasty ($n = 9$), 2) surgery of lower limb before follow-up ($n = 3$), 3) extreme pelvic rotation ($n = 1$) and 4) missing or destroyed original radiographs ($n = 30$). Thus, forty-nine patients were included in the study 42 males and seven females (Figure 1).

The mean age at onset was 6.0 (SD 2.0) years with no statistically significant difference between males (6.0 years, SD 2.0) and females (6.0 years, 2.0). The right side was affected in 26 (53%) and the left side in 23 (47%) of the patients. The Thomas splint was used for 25 (SD 6) months (range, 9-38 months). Twenty-nine of 49 hips (59%) were Class I/II and 20 out of 49 (41%) Class III/IV/V. Age at follow-up was 53 (SD 4) years (range, 44-63 years) for both genders and the patients were followed up 47 (SD 5) years (range, 33-56 years) after the onset of their disease.

Control group

The control group consisted of age- and gender-matched control persons obtained from The Copenhagen City Heart Study, Osteoarthritis Substudy [7]. The ratio of LCPD patients to control subjects was 1:2. Radiographs for the control group were obtained with the patient standing and standardized with a tube to film distance of 120 cm.

Requirements for radiographs

Pelvic rotation was assessed using Tönnis foramen obturator index, where maximum horizontal width of the right obturator foramen was divided by that of the left obturator foramen [16]. Extreme pelvic rotation was present when the foramen obturator index was <0.7 or >1.8 [6].

Radiographic parameters

We measured the CE angle (Figure 2), FHEI (Figure 3) and the AA angle (Figure 4) in AP radiographs of the pelvis. The measurements were defined as dysplastic when the CE angle was ≤ 20 degrees [17], FHEI was $< 75\%$ [3] or AA angle > 10 degrees [3].

Intra-observer reliability

Intra-observer reliability of measurements of Stulberg group classification and the radiographic measurements were assessed by blinded re-reading of a subset of 20 radiographs four months after the first reading. All radiographs were evaluated by one of the authors (LF).

Statistical methods

A normality test, using probit plots, showed that all data were normally distributed. Thus data are presented as means.

Intra-observer agreement for the categorical variable was assessed using the weighted kappa coefficient. A kappa of 0.21 to 0.40 is considered to be fair; 0.41 to 0.60 moderate; 0.61 to 0.80 good and 0.81 to 1.0 almost perfect [9]. For the numerical variables, Bland Altman limits of agreement were assessed.

To evaluate if LCPD patients had a significantly increased prevalence of dysplastic changes compared with the control group, we used exact logistic regression analysis with the cluster option in STATA to account for the matching. The difference between the mean measured radiographic

values in the LCPD patients and the control group was evaluated by linear regression analysis by means of the STATA cluster option. All statistical analyses were performed with the STATA® version 10.0 statistical software (StataCorpLP, College Station, TX).

Results

Intraobserver reliability

The intra-observer reliability was 0.93 and thereby almost perfect for the Stulberg classification. The limit of agreement was acceptable for the CE angle, AA angle and FHEI. The Bland Altman plots are presented in Figure 5.

Prevalence of hip dysplasia

In the affected hip in Class I/II 11 out of 29 (38 %) had a dysplastic hip defined as CE angle ≤ 20 degrees ($p < 0.0001$ [OR= 29 (95%CI 4.6-infinite)]) (Table 1a) and 11 out of 20 (55 %) in Class III/IV/V ($p < 0.0001$ [OR= 31 (95%CI 5.0-infinite)]) (Table 1c) compared with 1 out of 98 (1 %) in the control group. The odds of having reduced acetabular coverage of the femoral head was increased four-fold in the affected hip in Class I/II ($p = 0.02$ [OR= 4 (95%CI 1.1-17.9)]) (Table 1a) and twenty-fold in Class III/IV/V ($p < 0.001$ [OR= 20 (95%CI 2.9-infinite)]) (Table 1c) compared with the controls. The odds of having a dysplastic hip defined as a AA angle > 10 degrees, was increased seven times in the affected hip in Class I/II ($p < 0.01$ [OR= 7 (95%CI 1.7-37.1)]) (Table 1a) and 34 times in Class III/IV/V ($p < 0.0001$ [OR= 34 (95%CI 5.7-infinite)]) (Table 1c) compared to the control group.

For the non-affected hips in Class I/II and Class III/IV/V no significant difference in prevalence of dysplastic hips were found compared with the control group (Table 1b and Table 1d).

Radiographic values

In the affected hip the mean CE angle in Class I/II was 25 degrees ($p < 0.001$) and in Class III/IV/V 21 degrees ($p < 0.0001$) compared with 32-33 degrees in the control group (Table 2a and 2c). No significant difference in FHEI was found in Class I/II compared with the control group. In Class III/IV/V FHEI was decreased to 76 per cent compared with 84 per cent in the control group ($p < 0.01$) (Table 2a and 2c). The AA angle in the affected hip was significantly increased to nine degrees in Class I/II and 13 degrees in Class III/IV/V hips compared with four degrees in the control group (Table 2a and 2c). For those hips which were defined as dysplastic no statistically

significant difference of the radiographic values between Class I/II and Class III/IV/V were found (Table 3). However, there was a tendency towards less head coverage in Class III/IV/V compared with Class I/II ($p=0.06$).

In the non-affected hip in Class I/II no difference of the mean value of the dysplastic radiographic parameters was found (Table 2b). In the non-affected hips in Class III/IV/V the CE angle was decreased from 33 degrees in the control group to 29 degrees in the LCPD patients ($p<0.01$), furthermore the AA angle was significantly increased ($p=0.01$) to seven degrees compared with four degrees in the control group (Table 2d).

Discussion

Previous long-term reports have described the prevalence of osteoarthritis and the need for total hip replacement [4,10,11,15,18], while the prevalence of hip dysplasia in LCPD to our knowledge is unknown. The current case-control study aimed to evaluate whether nonoperatively treated patients with LCPD (1) had an increased prevalence of hip dysplasia in the affected and non-affected hip, compared with a control group, and (2) to compare the absolute values of Wiberg's centre-edge angle (CE angle), the acetabular index angle (AA angle) and femoral head extrusion index (FHEI) in LCPD patients and a control group.

We evaluated the prevalence of hip dysplasia and the dysplastic changes in LCPD patients by using well-known radiographic parameters. The position of the femoral head to the acetabular cavity was assessed using the CE angle and the FHEI. The acetabular slope was assessed by the AA angle. The strengths of our study were firstly that the same conservative treatment regime with a Thomas splint was applied to all the children regardless of gender, age at onset and degree of femoral head involvement. The Thomas splint does not fix the hip in a contained position, but reduces the weight on the hip joint [8] and results in a course close or identical to the natural history of the disease [1]. Secondly, a gender- and age-matched control group was obtained from The Copenhagen City Heart Study [7]. Thirdly, we included only patients with limited pelvic rotation as it has been shown to affect the measurement of the CE angle [6]. Finally, the revised Stulberg classification was used as well as radiographic parameters with high inter- and intraobserver reliability [5,13]. We found almost perfect agreement with the Stulberg classification and acceptable inter-observer reliability for the CE angle, FHEI and AA angle.

There are limitations in our study. First, the study is based on radiographic findings and the clinical status of the patients was not evaluated. Second, our study is limited by a small number of patients.

We had to exclude nine patients due to total hip replacement. Radiographs before surgery were available for three of these patients. Two of the patients having total hip replacement had hip dysplasia while one patient had no sign of dysplasia. This indicates that LCPD patients having total hip replacement due to hip pain might suffer from hip dysplasia.

Dysplastic changes in the hip might result in an incongruent joint expressed as coxa magna and a shallow acetabulum. In the presence of coxa magna, the radius enlarges and the centre of the femoral head moves laterally. In a lateral deficient acetabulum, this will decrease the CE angle as well as FHEI. In contrast, the measurement of the AA angle is independent of the presence of coxa magna. Except for patients in Stulberg Class I, all LCPD patients have coxa magna, hence we consider the AA angle as the most valuable measurement of dysplasia in LCPD patients. In the current study the prevalence of hip dysplasia in the affected hip was minimum 40% in Class III/IV/V hips compared with maximum 13% in the control group. This could be explained by the presence of a deformed ovoid or flat femoral head or coxa magna. However, we also found that hips with a spherical head, both in Class I (without coxa magna) and in Class II (with coxa magna), were dysplastic. This suggests that hip dysplasia is not only a result of coxa magna but also a change in the acetabulum.

Overall in the affected hips the CE angle and FHEI were decreased and the AA angle increased regardless of the Stulberg Class compared with the control group. We were not able to evaluate whether the tendency towards hip dysplasia were due to primary changes in the femoral head affecting the acetabulum or vice versa. A recent study has shown that the changes in the femoral head occurred first followed by changes in the acetabulum [14], suggesting that the acetabulum moulds partly to the femoral head. In the current study, the dysplastic hip changes occurred in both Class I/II and Class III/IV/V hips. Since no significant difference between the radiographic measurements was found regarding Stulberg Class in the dysplastic hips, it seems that presence of disease, rather than severity of disease, affects the morphology of the hip joint.

Surprisingly, the non-affected hips in Class III/IV/V had also decreased CE angle and increased AA angle compared with the control group. Arie *et al.* [2] found that the non-affected hips in children with LCPD show anterior and lateral flattening of the femoral head, indicating that the non-affected hip can also become dysplastic during the active phase of the disease. Murphy *et al.* [12] suggest that radiographic changes might be explained by the affected leg being shorter than the non-affected, causing increased adduction of the femoral head and thereby less acetabular coverage. In

the current study the radiographic changes were only present in the severe Classes, which suggest that the non-affected hip is affected anyhow.

In conclusion, this study demonstrates that LCPD patients have a significantly increased prevalence of hip dysplasia in the affected hip regardless of Stulberg Class. In contrast the prevalence of the non-affected hip was similar to the control group. The radiographic parameters in the affected hip and in the non-affected hip in Stulberg Class III/IV/V were different compared with the control group.

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Figure 1. Diagram of patients in this retrospective study (n, number of patients).

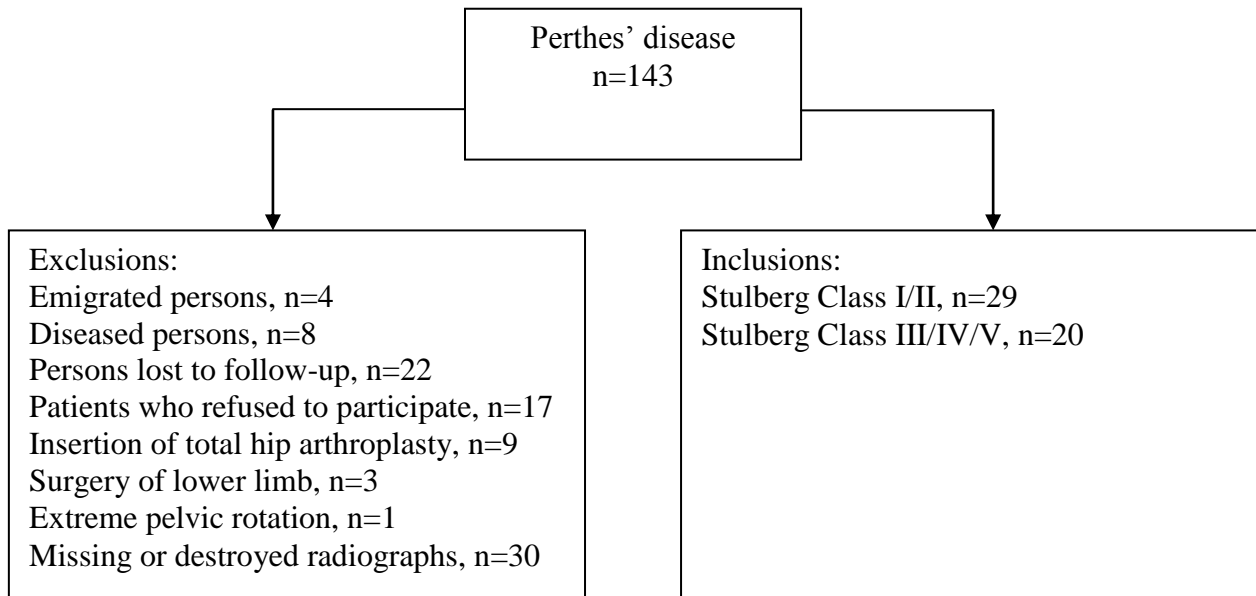


Figure 2. The CE angle of Wiberg designates the angle between a line perpendicular to a horizontal line through the femoral head centre (a) and a line from the femoral head centre to the lateral edge of the acetabular weight-bearing surface (b). The horizontal line was drawn at the lower point of the tuber ischii.

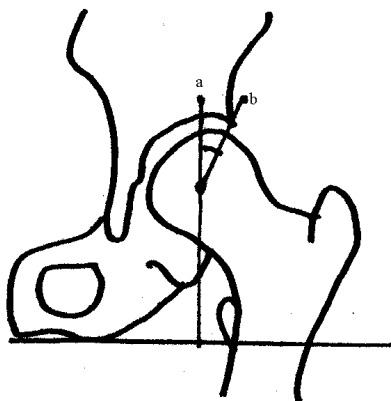


Figure 3. Femoral head extrusion index (FHEI). A horizontal line is drawn at the lower point of the tuber ischii. The distance perpendicular from the medial border of the femoral head and the lateral border of the weight-bearing surface of the acetabulum is measured (A). The distance from the medial border of the femoral head and the lateral border of the femoral head is measured (B).

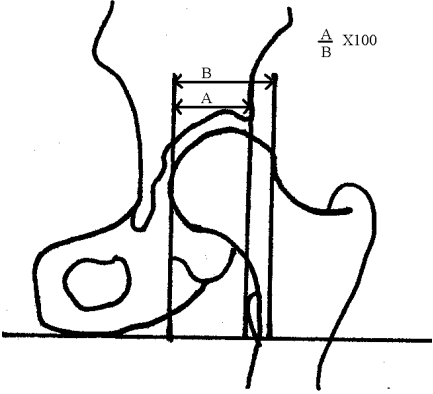


Figure 4. The acetabular index angle is measured as the angle between a line from the lateral edge of the acetabular weight-bearing surface to the medial sclerotic line of the acetabulum (a) and a horizontal line parallel to a line at the lower point of tuber ischii (b).

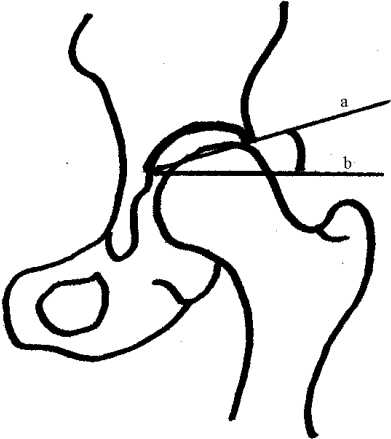
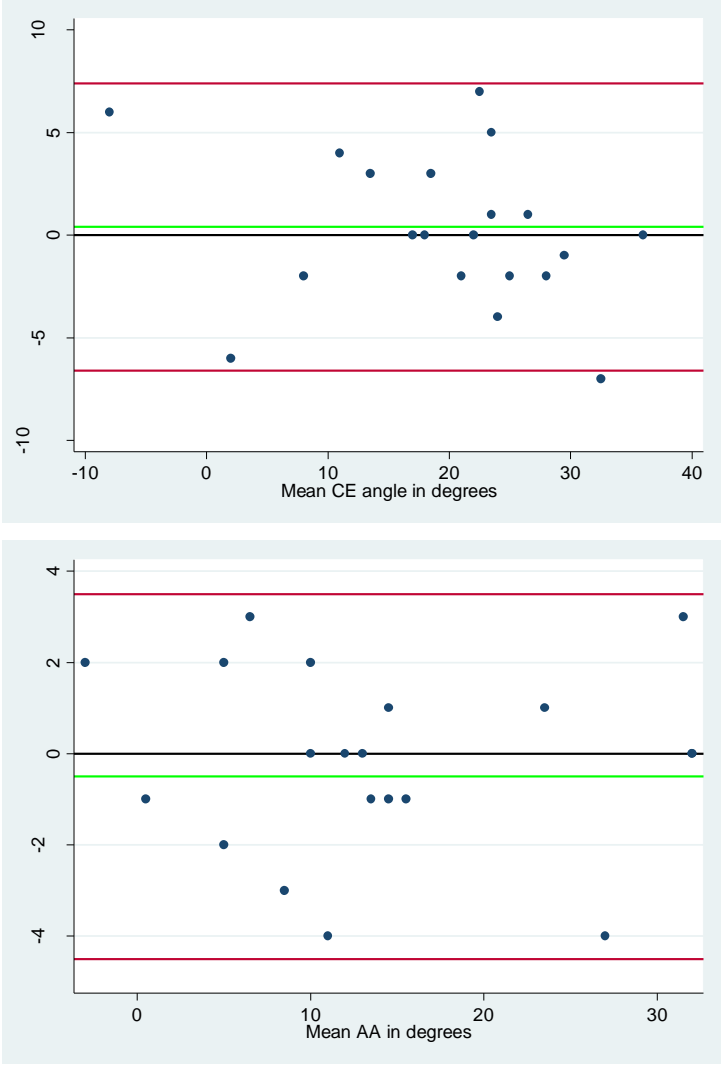


Figure 5. Bland Altman plot. The average difference between the first reading and the re-reading of the radiographic parameters (green line) as a function of the mean radiographic parameters are presented. The red lines represent the 95% limits of agreement. $y=0$ (black line) represent line of perfect average agreement.



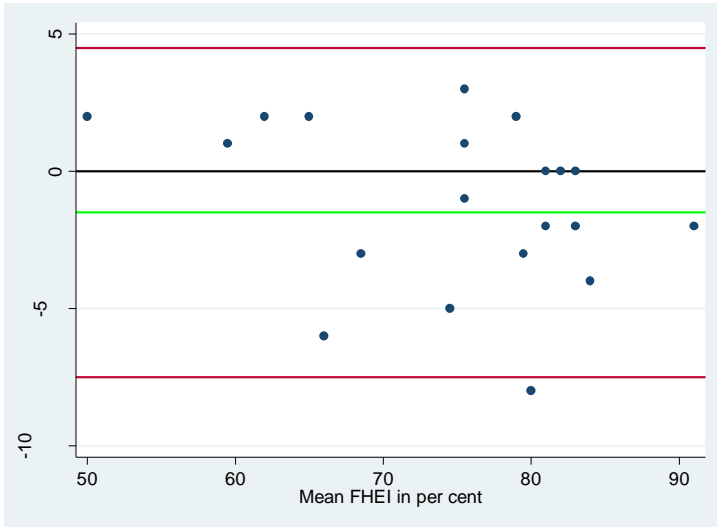


Table 1. Prevalence of dysplastic hips in LCPD patients and laterality-, gender-, and age-matched controls. Total number of LCPD/control hips (n), number of hips with dysplasia (N), percentage of hips with dysplasia (in brackets), odds ratio (OR) and 95% confidence interval (95%CI) are presented.

Table 1a. Stulberg Class I/II				Table 1b Stulberg Class I/II			
	Affected hips n=29	Control hips n=58	p-value		Non-affected hips n=29	Control hips n=58	p-value
CE $\leq 20^\circ$	N=11 (38%) OR 29 95%CI 4.6-inf	N=1 (2%)	<0.0001	CE $\leq 20^\circ$	N=2 (7%) OR 2 95%CI 0.1-27.6	N=2 (4%)	0.60
FHEI <75%	N= 11 (38%) OR 4 95%CI 1.1-17.9	N=9 (16%)	0.02	FHEI <75%	N=1 (3%) OR 1 95%CI 0.0-19.2	N=2 (3%)	1.00
AA >10 $^\circ$	N=12 (41%) OR 7 95%CI 1.7-37.1	N=7 (12%)	<0.01	AA >10 $^\circ$	N=1 (3%) OR 1 95%CI 0.0-8.3	N=3 (5%)	1.00
Table 1c Stulberg Class III/IV/V				Table 1d. Stulberg Class III/IV/V			
	Affected hips n=20	Control hips n=40	p-value		Non-affected hips n=20	Control hips n=40	p-value
CE $\leq 20^\circ$	N=11 (55%) OR 31 95%CI 5.0-inf	N=0 (0%)	<0.0001	CE $\leq 20^\circ$	N=3 (15%) OR 6 95%CI 0.5-315.0	N=1 (3%)	0.11
FHEI <75%	N=8 (40%) OR 20 95%CI 2.9-inf	N=2 (5%)	<0.001	FHEI <75%	N=3 (15%) OR 2 95%CI 0.2-12.3	N=4 (10%)	0.67
AA >10 $^\circ$	N=13 (65%) OR 34 95%CI 5.7-inf	N=1 (13%)	<0.0001	AA >10 $^\circ$	N=4 (20%) OR 2 95%CI 0.4-15.9	N=4 (10%)	0.42

p-value for comparison of number of patients with abnormal radiographic parameters between LCPD patients and control persons.

Table 2. Absolute values of radiographic parameters divided in Stulberg Class I/II and Stulberg Class III/IV/V in affected and non-affected hips compared with a laterality-, gender- and age-matched control group. The mean values, standard deviation (in brackets) followed by 95% confidence intervals are presented.

Table 2a Stulberg Class I/II				Table 2b Stulberg Class I/II			
	Affected hip n=29	Control n=58	p-value		Non-aff. hip n=29	Control n=58	p-value
CE angle in degrees	25 (9);22-28	32 (9);31-34	<0.001	CE angle in degrees	31 (6);28-33	32 (7);30-34	0.39
FHEI in %	79 (9);75-82	82 (6);81-84	0.09	FHEI in %	85 (6); 83-88	83 (7);82-85	0.27
AA angle in degrees	9 (7);6-12	4 (5); 2-5	<0.01	AA angle in degrees	5 (5);3-6	3 (5);2-4	0.23
Table 2c Stulberg Class III/IV/V				Table 2d Stulberg Class III/IV/V			
	Affected hip n=20	Control n=40	p-value		Non-aff. hip n=20	Control n=40	p-value
CE angle in degrees	21 (10);16-25	33 (5);31-35	<0.0001	CE angle in degrees	29 (7);25-32	33 (6);31-35	<0.01
FHEI in %	76 (10);71-80	84 (7);81-86	<0.01	FHEI in %	82 (10);77-87	84 (7);82-86	0.48
AA angle in degrees	13 (8);10-17	4 (4);3-5	<0.0001	AA angle in degrees	7 (4);5-9	4 (4);2-5	0.01

p-value for comparison of mean values between LCPD patients and control persons.

Table 3. The mean values, standard deviation (in brackets) followed by 95% confidence intervals are shown for the radiographic parameters for those hips (n) which were dysplastic in LCPD patients in the affected hip.

	Stulberg Class I/II	Stulberg Class III/IV/V	p-value
CE angle	n=11 16 (4); 13-19	n=11 15 (8); 10-20	0.71
FHEI	n=11 70 (4); 67-73	n=8 65 (7); 59-71	0.06
AA angle	n=12 17 (4); 14-19	n=13 17 (6); 14-21	0.67

p-values for comparison of mean values between LCPD patients with hip dysplasia in Stulberg Class I/II compared with patients with hip dysplasia in Stulberg Class III/IV/V.