

The efficacy of surgical approach on patient-reported outcomes, gait and hip muscle strength in patients with hip osteoarthritis after total hip arthroplasty

A comparison of the posterior approach with the lateral approach – COMPALA

PhD Thesis

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December 2015

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Acknowledgement

This PhD thesis and the associated individual manuscripts would not have been possible without the collaboration, advice, assistance and support from a variety of people and institutions.

Especially I owe my gratitude to all the dedicated patients who participated in this study. They invested both their time and effort in carefully filling out questionnaires and attending timely meetings for gait analyses. Thank you!

I wish to thank my supervisors:

Professor Søren Overgaard, for your great enthusiasm for the project from the very first day. For your ability to open doors, making this project possible and for your guidance into the world of scientific thinking and doing.

Associate Professor Anders Holsgaard-Larsen and Assistance Professor Carsten Jensen, for your guidance into the –sometimes mysterious- world of biomechanics and for always having your door open, making time for good discussions and keeping me on the right track. Your support defiantly improved my work.

Leif Broeng, for introducing me to the world of hip arthroplasty surgery, for inspiring me to do research within this field, and for always being optimistic, encouraging, participative and for making things happen.

I also owe my gratitude to Kim Schantz and the Department of Orthopaedic Surgery and Traumatology, Køge Hospital, who believed in this project and in every way showed great willingness to make it possible.

No surgery without surgeons! I owe a very special thanks to:

René Kirchhoff-Jensen and Jörg Dominik Adam for your time and commitment into this project. I really appreciate all the trips both of you took across the bridge.

Ole Ovesen, Hans Christian Kærlev and Morten Foged Bøgehøj, with whom working with always was a pleasure. Thank you for your skilful supervision and good company in the outpatient clinic.

I would also like to thank all the people behind the scenes:

I do not know what I would have done without Annie Gam-Pedersen. You kept all the patients, the surgeons - and me!- on a short but always very caring leash. Not every orthopaedic department is blessed with a secretary as dedicated as you, Marianne Larsen, but luckily we are! Rasmus Skov Sørensen and Dennis Brandborg Nielsen, you both ensured high quality data from the gait laboratory and kept the wheels running when I was not there. Suzanne Capell for critically proofreading my thesis and manuscripts.

To all the staff at the OR and O3 in the Department of Orthopaedics and Traumatology, Odense University Hospital, you all showed a great interest in the project.

To my research fellows, you always found time and room for fruitful discussions and a good laugh with 'the girl from out of town'.

To those at home:

I am grateful for my family and friends- you are always there when I need you- especially when it gets really tough. To Henrik for being such a good friend- despite everything.

To my lovely children Freja and Valdemar: 'You make me smile every day!'

Finally, to you Dennis, I could say a lot. I think I will start saying: 'Thanks for your seemingly endless patience with me', and continue by saying: 'You changed my life' and end by saying: 'Jeg elsker dig'.

Thank you, each and every one of you!

Signe Rosenlund

December 2015

Abbreviations

ASA = American Society of Anaesthesiology Classification
ADL = Activity of daily living
BMI = Body mass index
CI = Confidence interval
DA = Direct anterior approach
EQ-VAS = Visual analogue scale of EQ-5D
EQ-5D = EuroQoL-5D-3L
EQ-5D-3L-index = Global health index with a weighted total value for health-related quality of life
GDI = Gait Deviation Index
Hgb = Haemoglobin
HHS = Harris Hip Score
HOOS = Hip disability and Osteoarthritis Outcome Score
HOOS-Physical Function = HOOS-Physical Function Short-Form
HOOS-Pain = HOOS subscale of pain
HOOS-QOL = HOOS subscale of quality of life
iMVC = Isometric maximal voluntary contractions
ITT = Intention-to-treat analysis
LA = Lateral approach
MCAR = Missing completely at random
MCID = Minimal clinically important difference
MCII = Minimal clinically important improvement
mGDI = mean GDI score calculated on the basis of five trials of the affected limb
NNT = Numbers Needed to Treat
NRS = Numeric rating scale for pain
OA = Osteoarthritis
OHS = Oxford hip score
OMC = Orientation–Memory–Concentration Test
PA = Posterior approach
PASS = Patient-acceptable symptom state
PRO = Patient-reported outcome
PROM = Patient-reported outcome measure
RCT = Randomised controlled trial
ROM = Range of motion
RR= Relative risk
SF-36 = Short Form (36) Health Survey
THA = Total hip arthroplasty
UCLA = University of California Los Angeles activity score
WOMAC = Western Ontario and McMaster Universities Arthritis Index
3-DGA = Three-dimensional gait analysis

List of papers

The thesis is based on 4 papers:

Protocol

‘The effect of posterior and lateral approach on patient-reported outcome measures and physical function in patients with osteoarthritis, undergoing total hip replacement: a randomised controlled trial protocol’. Signe Rosenlund, Leif Broeng, Carsten Jensen, Anders Holsgaard-Larsen and Søren Overgaard. BMC Musculoskeletal Disorders 2014, 15:354

Study 1

‘The Gait Deviation Index is associated with hip muscle strength and patient-reported outcome in patients with severe hip osteoarthritis - a cross-sectional study’. Signe Rosenlund, Anders Holsgaard-Larsen, Søren Overgaard and Carsten Jensen. PLoS ONE 11(4): e0153177. doi:10.1371/journal.pone.0153177

Study 2

**‘Patient-reported outcome after primary total hip arthroplasty through modified direct lateral or posterior approach in 80 patients with 12-months follow-up
A randomised controlled trial’.** Signe Rosenlund, Leif Broeng, Anders Holsgaard-Larsen, Carsten Jensen and Søren Overgaard.

In review at ‘Acta Orthopaedica’, December 2015

Study 3

**‘The efficacy of modified direct lateral versus posterior approach on gait function and hip muscle strength after primary total hip arthroplasty at 12 months follow-up
An explorative randomised controlled trial’.** Signe Rosenlund, Leif Broeng, Søren Overgaard, Carsten Jensen and Anders Holsgaard-Larsen

In review at ‘Clinical Biomechanics’, January 2016

Introduction

Hip osteoarthritis

The World Health Organization estimates that osteoarthritis (OA) is one of the leading causes of years lost to disability worldwide and one of the most common chronic diseases of the musculoskeletal system [1, 2]. This means there is a great need to improve the treatment for OA.

OA is characterised by a progressive degeneration of the entire joint involving the cartilage, ligaments, and underlying bone. Hip OA is classified into two subgroups. Primary (idiopathic) OA is by far the most common. However, the aetiology is to a large extent unknown. Secondary OA has a known aetiology (e.g. previous fracture, infection, congenital disease, malformation and dysplasia) and is less common.

Prevalence

In a US population aged ≥ 45 years it was estimated that 10% had symptomatic hip OA and 2.5% had moderate/severe radiographic hip OA [3] and it is well recognised that the prevalence increases with age [3, 4]. Up to 40% of people aged ≥ 65 in the United Kingdom suffers from symptoms associated with hip or knee OA [5]. The lifetime risk of developing symptomatic hip OA is estimated to be 25% [6].

Symptoms

Hip OA symptoms are dominated by pain from the diseased joint accompanied by joint stiffness and reduced physical function. In the early stages, symptoms are present during use of the joint and relieved when at rest. Later, the symptoms progress to being present at rest and can eventually disturb sleep. Hip pain is one of the major causes of gait disability and difficulty in climbing stairs in the elderly population in both Europe and the US [7]. Collectively, symptoms from OA affected joints lead to a marked decrease in the quality of life [8] and an increase in mortality compared with healthy individuals [9].

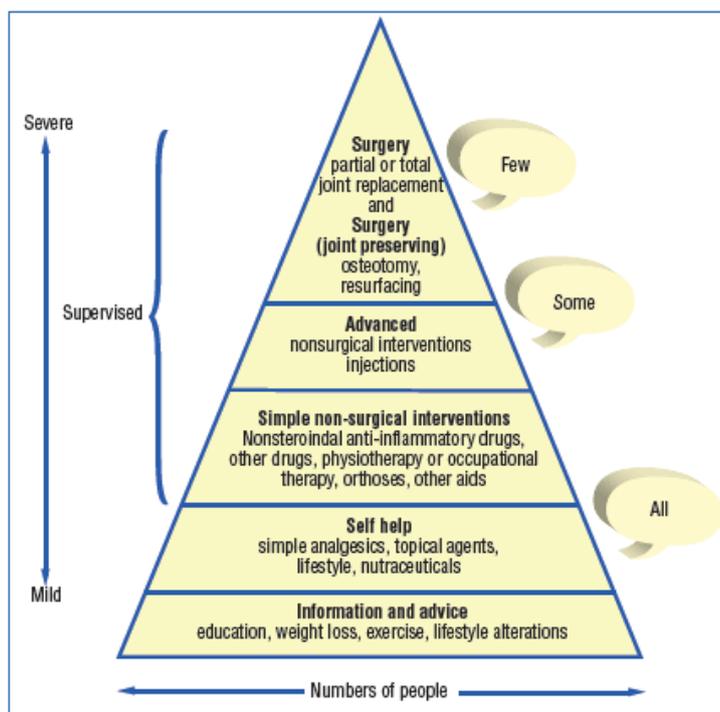
Diagnosis

The clinical diagnosis of hip OA is based on the history of symptoms often with gradual deterioration in combination with a clinical examination where passive motion, joint stiffness and pain during motion are assessed and finally a hip radiograph where joint space narrowing, osteophytes, bony sclerosis and cysts present as hallmarks of OA [10].

Treatment

There is currently no cure for hip OA. All treatment strategies aim at relieving the symptoms. Osteoarthritis Research Society International (OARSI) recommends that the treatment be divided into three stages [7]. The first stage involves non-pharmacological and non-surgical treatments, which should be offered to all patients. It consists of education, coping strategies, exercise and weight loss (when indicated). The second stage treatment is for the group of patients with progressive symptoms and includes pharmacological treatments with paracetamol and/or non-steroidal anti-inflammatory drugs, walking aids, physiotherapy and steroid joint injection. The last stage is surgical treatment with a THA and should only be offered to patients where first and second stage treatment does not reduce symptoms sufficiently [7]. Figure 1 illustrates the treatment pyramid. Total hip arthroplasty (THA) surgery is performed to treat primary OA in 80% of all cases in Denmark [11].

Figure 1. Principles of hip OA management



Pathogenesis and management of pain in osteoarthritis. *Lancet* 2005; 365: 965–73.
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Total hip arthroplasty

The success

THA surgery is a well-recognised treatment offered to patients with hip OA [12]. In the 1960s, Sir John Charnley's design of a low friction arthroplasty revolutionised management of patients with OA [13] with good long-term results [14, 15]. Due to its great success, THA has been called '*The operation of the century*' [16].

THA is one of the most frequently performed procedures in orthopaedic surgery [17]. Worldwide, over a million patients receive a THA each year. In the US, about 427,000 primary THAs with any indication are performed every year [17]. In Denmark almost 9,000 THAs are performed [11] and in Sweden over 16,000 THAs are performed [18], and the numbers are expected to increase due to the growing elderly population and a decrease in mean age at surgery [17, 18].

Conventional outcomes

Conventional outcomes regarding THA surgery are: revision rate including causes of revision (e.g. aseptic loosening, dislocation and infection), survival rates of different prosthetic component concepts, surgically related complications (e.g. perioperative fractures, infections, need for blood transfusion, deep vein thrombosis and pulmonary embolism), surgeon-reported outcomes [19] and mortality rate.

But with low mortality rate [20], acceptable revision rates and increasing survival rates of the prosthesis [11, 21] a shift from using conventional outcome to patient-reported outcome measures (PROM) has increased over the last decade. This partly because it has been shown that there is a discrepancy between conventional surgeon-reported outcomes and patient-reported outcomes (PROs) [22, 23].

Patient-reported outcomes

Despite great success with THA surgery, the PROs have revealed that 15 to 30% of the patients reported little or no improvement or were unsatisfied with the results [21]. Chronic pain was reported by 12% of the patients after THA in Denmark [24] and patients did not accomplish the same level of physical function compared with the general population [25, 26]. According to the Danish Hip Arthroplasty Register 2005, 6% of patients with primary THA were 'unsatisfied' or 'not completely satisfied' after a minimum of 6 months follow-up [27],

and in Sweden up to 14% of the patients were not satisfied post-operatively [20]. One factor influencing the PROs may be the surgical approach [28, 29].

Factors with influence on outcome after THA

However, several factors have an influence on both the conventional outcomes and the PROs after THA surgery. Patient-related factors like co-morbidity, the diagnosis leading to THA surgery, gender and age, all play a role in the outcome [11, 18, 30, 31]. Surgeon-related factors like experience and the volume of surgeries performed each year may have an influence [32, 33]. And finally, surgically-related factors like choice of prosthetic concept (e.g. cemented versus cementless concepts) and the surgical approach may also influence the outcome [11, 34]. In this thesis we will focus on the influence the choice of surgical approach may have on both patient-reported and objective outcomes.

Surgical approach

The choice

The choice of surgical approach is an important part of any pre-operative planning in orthopaedic surgery.

The surgical approach must enable sufficient overview of important anatomical structures. Thus the acetabulum and the proximal femur must be visible and accessible to facilitate optimal positioning of the cup and stem [35, 36]. At the same time, it must facilitate sparing of vital anatomical structures (e.g. the sciatic nerve and arteria femoralis). It is important that the approach induces limited surgical trauma to the tissue (muscles, tendons, joint capsule) to preserve the hip joint's stability, function and muscle strength [37]. However, it should be possible to extend the exposure per-operatively in difficult cases [37].

Furthermore, the surgery must be carried out within a reasonable time period to lower risk of infection, bleeding and other surgically-related complications but also to make the treatment cost-effective.

The need for special equipment and the number of personnel required to carry out the surgery must be considered. The approach should not lead to extensive post-operative restrictions delaying mobilisation and rehabilitation [38] and must allow for later revision. Last but not least, the approach should provide satisfying outcomes for the patient.

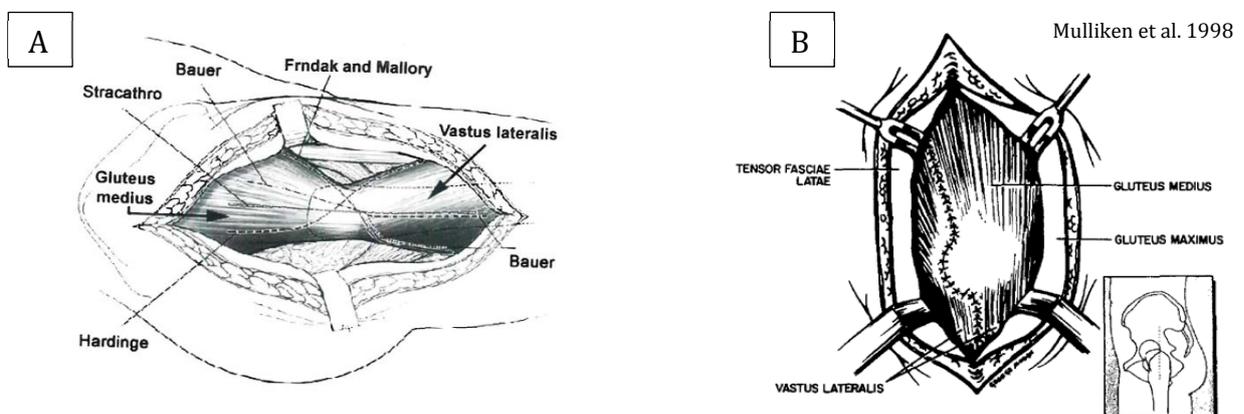
The choice of approach is often based on surgical traditions within a country, region or surgical department and on the surgeon's personal preference [39].

Nomenclature

A variety of surgical approaches has been described and many are frequently used today. However, the nomenclature can be confusing due to many synonyms and inconsistent use of them, especially for the lateral approach [40]. Furthermore, many studies have insufficient descriptions of the approach [41-43]. This complicates the comparison of outcomes between approaches [40, 44].

Table 1 describes five different conventional surgical approaches to the hip and their relation to important anatomical structures. Figure 2 shows the many variations of the muscle split performed during the lateral approach. These variations are the cause of many of the synonyms. The different impact on soft tissue and muscles during surgery are hypothesised to result in different risk of complications [44].

Figure 2. A) Variations in the gluteus medius and vastus lateralis split during the lateral approach. B) The gluteus medius and vastus lateralis split during the modified direct lateral



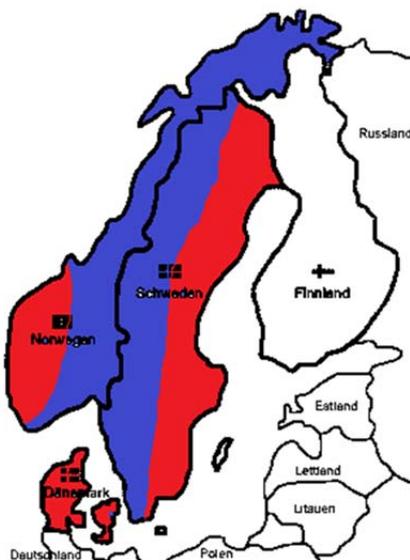
The posterior approach is hypothesised to increase the risk of dislocation and risk of revision due to dislocations because of the surgically induced trauma to the posterior stabilising structures [44, 45]. In contrast, the surgically induced trauma on the hip abductor muscles performed during the lateral approach is hypothesised to cause hip abductor muscle weakness [46, 47], limping [28, 40, 48], and as a consequence of these potential adverse effects, the PROs may be influenced negatively [28, 29].

A recent worldwide survey revealed that the surgeons' choice of approach was divided between the posterior approach (PA) (45%) and the direct lateral approach (LA) (42%), followed by the direct anterior approach (DAA) (10%) and others (3%). North American surgeons favoured the PA more than European surgeons (69% compared with 36%, respectively) [49].

In the Scandinavian countries the choice of surgical approach is registered in the national arthroplasty registries and is divided mainly between two approaches. In Denmark, the posterior approach is favoured in most cases (95%), whereas in Norway the lateral approach is favoured (75%). In Sweden, a more equal use of PA and LA are seen (60% vs. 40%, respectively) [11, 50],

Figure 3.

Figure 3. The distribution of PA and LA in the Scandinavian countries



Since most THAs are performed with the posterior or the lateral approach worldwide and also in Denmark, the focus in this thesis will be on those two approaches. Descriptions of the two approaches can be found in section 'Intervention set-up', page 30.

Table 1. Description of five conventional surgical approaches

Surgical approach	Synonyms*	Authors*	Anatomical description of approach	Anatomical structures at risk
Posterior (PA)	Posterolateral Gibson Moore Southern hip exposure Gluteus maximus split	Langenbeck 1874 Gibson 1950 Moore 1959 Hunter 1986	Blunt dissection of gluteus maximus. Detachment of the small external rotators. Incision of the posterior part of the hip capsule. May include capsular repair and re-insertion of the small external rotators.	The sciatic nerve Posterior stabilizing tissue (joint capsule and small external rotators)
Lateral (LA)	Direct lateral Hardinge Stracathro approach Abductor split Translateralt Gammer Modified direct lateral approach	Bauer 1979 Hardinge 1982 McLauchlan 1984 Gammar 1985 Frndak and Mallory 1993 Mulliken 1998	The anterior one-third of the gluteus medius and the gluteus minimus tendon insertions on the greater trochanter are split longitudinally and sharply separated from the greater trochanter. Vastus lateralis is split and detached anteriorly in the combined tendon and periosteum with the gluteus medius. Many variations of the gluteus medius muscle split along with vastus lateralis are described, Figure 2.	The superior gluteal nerve The abductor muscles
Lateral transtrochanteric (LA+TO)	Lateral approach with osteotomy	Charnley 1961	The gluteus medius and vastus lateralis are visualised. The osteotomy is performed after identification and freeing the borders of the gluteus medius, and elevation of the origin of the vastus lateralis. The anterior capsule is exposed by external rotation of the femur and divided The osteotomised fragment is reflected proximally and a capsulectomy is performed.	The superior gluteal nerve The abductor muscles Non-union/displacement of the trochanteric osteotomy
Antero-lateral (ALA)	Watson-Jones	Watson-Jones 1936	Utilises the intermuscular interval between the tensor fasciae latae and the gluteus medius without any incision or dissection of the muscles	The superior gluteal nerve
Direct Anterior (DAA)	Direct anterior Smith-Petersen	Smith-Petersen 1949	Utilises the internervous and intermuscular interval between the muscles of sartorius, rectus femoris and iliopsoas on one side and the tensor fasciae latae on the other side	The lateral femoral cutaneous nerve

*The list of synonyms and authors may not be exhaustive

Surgical approach and patient-reported outcomes

Choosing the most optimal surgical approach regarding PROs would contribute to achieving a better treatment for thousands of patients. However, the literature reveals that evidence from level I studies comparing PA with LA is missing. Four registry-based studies and one prospective cohort study (level II evidence) have revealed a significant but small difference in favour of PA on varying PROMs. Only one randomised controlled trial (RCT) (level I evidence) has been performed, using the surgeon-reported outcome measure Harris Hip Score (HHS) as primary outcome and as secondary outcome, the Western Ontario and McMaster Universities Arthritis Index (WOMAC) which is a PROM was used [51]. They reported no significant difference between PA and LA after 3 months follow-up [51] Table 17, page 64 lists the studies that have evaluated the PRO after PA compared with LA. One systematic Cochrane review has been performed investigating potential differences between LA and PA, but they were not able to include PROs in the analysis, due to lack of studies [44].

The registry-based study by Amlie et al. 2014 also included evaluation of self-reported limping gait and found that twice as many patients in the LA group had limping gait compared with the PA group. They also showed that limping gait, irrespective of surgical approach, was associated with significantly reduced PROs measured on the Hip Disability and Osteoarthritis Outcome Score (HOOS) [28]. Furthermore a prospective study has shown that the gait measured with a 6-minute walk test was positively correlated with PROs measured on WOMAC and SF-36 [52]. Thus, the gait seems to also influence the PROs.

Gait function

Limping gait is a major concern after THA [37, 40, 48, 53, 54]. However; no clear definition of limping exists although it can be referred to as asymmetry in the gait [46]. A narrative review of the literature from 1970 to 2001 [40] reported a slightly higher prevalence of limping gait among LA patients 4%-20% versus PA patients 0%-16% [40]. But, the studies included were in general of lower quality, limping was measured with different methods often with low validity, thus making a direct comparison between studies difficult [40]. A more direct comparison between LA and PA was performed in the study by Amlie et al. 2014. They showed that 12% of PA patients had self-reported limping post-operatively compared with 24% of the patients in the LA group. But they also did not attempt to define limping gait.

Since limping gait is not well defined and gait function is difficult to measure due to the complexity of the biomechanics involving all major joints in the lower extremities in three planes, the three dimensional gait analysis (3-DGA) is often used to objectively assess gait function in patients with THA [55]. Several gait analysis studies have shown that THA patients do not achieve the same gait pattern as healthy controls [56-62]. A narrative review of these studies also revealed a large variety in the discrete variables reported. Thus 46 different 3-DGA variables were reported in the seven included studies (7 temporo-spatial, 18 kinematic, 21 kinetic) [55]. However, no consensus on which variables to report exist and only six variables (walking speed, stride length, sagittal hip range of motion, peak flexion moment, peak extension moment and peak abduction moment) were reported in three or more studies.

The number of discrete variables is numerous and it makes a coherent interpretation of the gait pattern difficult. Furthermore discrete variables lack the ability to evaluate the overall gait pattern or gait 'quality' throughout the entire gait cycle [63]. Therefore, there is an increasing interest in implementing a summary index that describes the overall gait 'quality' expressed as the degree of deviation from normality.

The Gait Deviation Index (GDI) has been proposed to simplify the kinematics of the lower limb during gait in one index ranging from 0 to >100, where an index ≥ 100 represents normal gait 'quality' [64]. GDI has previously shown improvements when used to assess the change in pre-operative to post-operative gait 'quality' in THA patients [65, 66] and has also been applied in other patient groups [67-71].

True validation of GDI in hip OA/THA patients is difficult since no gold standard exists for the measure of gait 'quality'. However, GDI has been validated against the Gross Motor Function Measure in cerebral palsy patients [72]. Research into associations between GDI as a measure of gait 'quality' and validated clinically important outcomes will improve the understanding of the clinical utility and application of GDI in research and in the clinical context. This has, to our knowledge, only been performed in patients with cerebral palsy and rheumatoid arthritis [70, 71, 73].

Three gait analysis studies have investigated gait pattern in patients operated on with PA compared with LA [43, 59, 74]. The studies by Madsen et al. 2004 and Whatling et al. 2008 classified patients based on discrete 3-DGA variables in comparison with healthy controls.

Both studies concluded that the LA patients had a more abnormal gait than the PA patients compared with healthy controls. The study by Queens et al. 2013 did not find any difference between the PA and LA groups at 12-month follow-up [74]. All three studies investigated varying discrete variables from the 3-DGA and they were based on small sample sizes of 10-14 patients in each group. None of the studies were randomised [43, 59, 74] and the evaluation of overall gait 'quality' was not performed.

Hip muscle strength

Several studies have shown that both patients with hip OA and patients after primary THA surgery have reduced hip muscle strength compared with healthy controls [46, 75-77].

Further, it has been shown that reduced lower limb muscle strength is a predictor of the onset of dependency in activities of daily living (ADL) and reduced physical function in elderly and knee OA patients [78, 79]. Therefore, it is important to investigate if the surgical approach has any influence on the post-operative hip muscle strength.

The Trendelenburg test was described as a clinical test for hip abductor function by Hardcastle and Nade 1985 [80], and is widely used as a surrogate measure of abductor muscle strength [81]. Three studies used the Trendelenburg test to compare the abductor muscle strength between the PA and LA [51, 81, 82]. They found a higher prevalence of a positive Trendelenburg test in the group of LA patients versus PA patients, indicating abductor weakness in the LA group. Also the narrative review of the literature by Masonis et al. 2002 reported a slightly higher prevalence of a positive Trendelenburg test in the LA patients (5.7%- 16%) compared with PA (4.7%-13%) [40]. However, the validity of the Trendelenburg test as a measure of abductor muscle strength has recently been questioned. Kendall et al. 2010 concluded that the magnitude of pelvic drop and hence a positive Trendelenburg test was poorly correlated to weak hip abductor muscles [83] and that the Trendelenburg test should not be used as a screening measure for hip abductor strength [84].

Table 2 shows five studies that have investigated the hip abductor muscle strength between PA and LA. The results vary greatly. The study by Winther et al. 2015 found significantly lower hip abductor muscle strength 6 weeks post-operatively in the LA group compared with the PA group [46]. Another study reported reduced hip abductor muscle strength in the operated leg compared with the unaffected leg in the LA group, but not in the PA group [47].

The other three studies did not report significant difference between the two groups [85-87]. None of the five studies were RCTs. Two of the studies measured the hip muscle strength with less reliable methods [85, 87], the study by Winther et al. 2015 measured the maximal muscle strength by a 'one-repetition maximum strength test' and, therefore, not an isometric muscle strength test. Lastly, the results in the study by Downing et al. 2001 may be influenced by a large drop-out rate on 27% [86]. Thus, no firm conclusion can be drawn about a difference in hip muscle strength after THA performed with PA compared with LA.

Table 2. Studies comparing hip abductor muscle strength in patients with PA versus LA

Study	Design	Number of patients	Diagnosis	Approach	Follow-up	Hip muscle strength	Results
Gore et al. 1982	Cross-sectional study	PA: 52 ALA: 33	Primary OA Fractures Avascular necrosis	PA- with no repair ALA- Watson-Jones	Mean 2.5 years	Isometric maximal abductor strength Compared with contralateral healthy leg	Significant difference between hip abductor strength in the operated and healthy leg in the ALA group No difference in the PA group
Barber et al. 1996	Cohort study	PA: 28 LA: 21	Primary OA	PA- with no repair LA- Hardinge	1 year	Manual testing-grade 0-5	No significant difference between groups
Downing et al. 2001	Prospective cohort	PA: 51 LA: 49	Primary OA	PA- with repair? LA- Hardinge	Pre-operatively 3 months 1 year	Isometric maximal abductor strength	No significant difference between groups
Kiyama et al. 2010	Cross-sectional study	PA: 40 LA: 38	Primary OA Avascular necrosis	PA- with repair LA- Frndak and Mallory	Mean 3.3 to 3.5 years	Isometric maximal abductor strength measured in a ratio compared with contralateral healthy leg Hand-held dynamometer with the patient in supine position	No significant difference between groups Decreased abductor strength compared with healthy leg in both groups
Winther et al. 2015	Prospective cohort study	PA: 19 LA: 21	Unilateral OA Unclear if all indications were included	PA- with repair LA- Hardinge	Pre-operatively 2 days 8 days 6 weeks 3 months	1 repetition maximal hip abduction strength tested with the patient in supine position	Significant difference up to 6 weeks between groups At 3 month no significant difference between groups

Motivation for this Ph.D.-thesis

As outlined above, the literature comparing PA with LA generally is of a lower evidence level and the optimal choice of surgical approach remains unclear. The extent to which the choice of surgical approach affects the outcome from a patient's perspective, the patients gait and hip muscle strength needs to be further investigated. Therefore, the motivation for this Ph.D. thesis was primarily to investigate if PA was superior to LA regarding improvements in PROs, gait function and hip muscle strength in a prospective RCT (evidence level I).

Secondarily, it was to investigate the application of the gait 'quality' index (GDI) in hip OA and THA patients.

Aims and Hypotheses of the Ph.D.-thesis

Protocol

The aim was to facilitate transparency and access in research, by *a priori* clearly describing and publishing the protocol for a randomised controlled trial to investigate the superiority of PA compared with LA.

Study 1

The aim was to investigate potential associations between gait 'quality' measured by GDI, hip muscle strength and PROMs in patients with severe primary hip OA.

We hypothesised that low hip muscle strength, high pain levels and impaired self-reported physical function and quality of life would be associated with reduced GDI scores.

Study 2

The primary aim of this trial was to evaluate the efficacy of two surgical approaches to THA on patient-reported physical function, and the secondary aims were to evaluate their efficacy on patient-reported pain, physical activity, limping and quality of life.

We hypothesised that patient-reported outcomes within the first year would improve more in patients receiving PA compared with LA surgery.

Study 3

The primary aim of this explorative randomised controlled trial was to evaluate the efficacy of PA compared with LA after THA on gait function and secondarily evaluate the efficacy on hip muscle strength.

We hypothesised that gait function measured with GDI, temporo-spatial parameters, kinematic variables and hip muscle strength would improve more in patients operated on with PA compared with LA at 12 months follow-up.

Methodological considerations

Protocol

It is highly recommended to describe and publish the protocol when initiating an RCT [88, 89]. This facilitates transparency and access to research [88]. Transparency is important in order to reduce selective reporting, to avoid changes in inclusion criteria during the study period and post hoc changes in the primary outcome, all of which reduces the fully understanding of a trial's validity [88]. Access to research protocols and results is important to secure the transparency of trial conduct, but also to avoid 'waste of research' when results are not published or replicated but knowledge already exists [88].

We therefore published a full study protocol and the study was registered at ClinicalTrials.gov no: NCT01616667 prior to inclusion of patients. This has facilitated a structured study with clearly defined primary, secondary and explorative outcomes. This thesis focused on the primary and secondary PROs and explorative outcomes from the 3-DGA. All of these outcomes were measured with 12 months follow-up. The remaining explorative outcomes including physical performance test and consumption of pain killers were measured with 3 months follow-up and will be analysed in forthcoming publications outside the scope of this thesis. In the following sections important aspects of the methodological choices will be discussed.

Study design

Study 1- cross sectional

A cross-sectional design was used in this study to investigate associations between the GDI and hip muscle strength, pain and PROs. A cross-sectional study can be conducted more quickly, since no follow-up is needed and can be used to generate hypotheses. These advantages were utilised in Study 1. This design has also been applied in studies investigating the association between the GDI and clinical outcomes in different patient groups [71, 90]. The design, nevertheless, has some disadvantages. A cross-sectional study provides only a 'snapshot' of the outcomes at one specific time point, hence no causal explanations can be based on the results [91].

Study 2 and Study 3- RCT design

As outlined in the introduction, only one RCT had been performed comparing LA and PA in patients receiving a primary THA and that study did not use a PRO as the primary outcome. A

RCT is considered the gold standard within medical research [92]. The merits of a RCT are to a large extent caused by the random allocation of patients to treatment.

First, the random allocation to treatment eliminates selection bias. Second, random allocation allows the assumptions that any difference in outcome between treatment groups is caused by change. Third, random allocation facilitates successful blinding to treatments both to the investigators and the participants, which reduces bias after assignment of treatments [92].

This study utilised balanced block randomisation [1:1], using a computer-generated list containing a sequence of one letter and one number: 'A' referring the patient to PA, 'B' referring the patient to LA. '1' referring the patient to participate in the gait analysis thus contributing with data on the GDI, and '0' referring the patient not to participate in the gait analysis (see CONSORT flow diagram from the protocol, [Appendix A](#)). We used block randomisation (4 blocks of 20 patients each) to prevent imbalance in the number of patients allocated to the two treatments at any time during inclusion which has been recommended for sample sizes <100 [93]. However, the blocks were large enough to conceal the allocation sequence from the principal investigator (SR), who enrolled patients into the study. As shown in the CONSORT flow diagram based on the actual enrolment (Figure 6, page 46) we succeeded in a balanced randomisation of 41 and 39 patients in the two groups.

The randomisation sequence was generated by a third person (JL) not otherwise involved in the trial. The letter and number combination was written on paper, folded and placed in sealed opaque consecutively numbered envelopes. The booking secretary opened the envelopes in the given order, and according to the content the patient was scheduled for surgery.

In the first three blocks, there was a 66% chance of being allocated to group 1 (gait analysis). Hence we were able to verify the initial sample size calculation based on pre-operative ungrouped results of the GDI for the first 20 actual gait analyses performed (see sample size page 39).

Blinding

Both the patients and the principal investigator (SR) who enrolled the patients and conducted the primary and secondary statistical analyses were blinded to treatment allocation throughout the study period (Studies 2 and 3).

The surgeons, operating theatre personnel, ward doctors, ward nurses and ward physiotherapists were not blinded due to the nature of the intervention and the surgery descriptions in the medical records. However, they were all informed about the project and were well aware of the importance of not discussing the intervention with the patients. Since all patients were treated with the same rehabilitation protocol, described in the Protocol [94], there was no need to discuss the specific intervention.

The patients were informed, prior to participation, that the type of intervention would not be revealed to them before the end of the study and the reason for blinding was carefully explained to them. Blinding of the principal investigator during the analyses was possible to maintain because of the use of project id numbers for all patients, recoding of the allocation sequence from letters to numbers and the nature of the self-reported outcomes. However, the data collector (the principal investigator, the project engineer (DBN) and project physiotherapists (RSS)) conducting the 3-DGA were not blinded to the scar at the hip, since marker placement on the hip was necessary. We are aware that a few patients may have guessed their intervention but we did not measure the success of blinding systematically in accordance with the CONSORT statement [92].

Population

The study population in all three studies was based on patients with unilateral primary hip OA scheduled for a primary cementless THA. Patients were enrolled in the trial according to well-defined inclusion- and exclusion criteria, Table 3. The selected age criterion between 45 and 70 years was based on two considerations. Patients under the age of 45 years are more likely to suffer from secondary OA and thus they constitute another patient group. All patients over the age of 70 years are in our department offered a total cemented prostheses and the trial was not designed to account for differences in prosthetic concepts.

Table 3. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Aged 45 to 70 years	Symptoms in several joints (hip, knee or ankle) with expected total joint arthroplasty within one year
Diagnosed with primary hip osteoarthritis (OA) or secondary OA due to mild hip dysplasia (center-edge-angle > 20 degrees)	Prior total joint arthroplasty at any joint (hip, knee or ankle) or major lower limb surgery, still causing symptoms
Scheduled for primary cementless* total hip arthroplasty	BMI > 35 (kg/m ²)
	Any physical disability preventing the patient from walking freely without walking aids
	Any neurological disease (e.g. cerebral thrombosis, Parkinson Disease) compromising walking ability
	Any severe medical condition compromising physical function (e.g. chronic heart failure, chronic obstructive pulmonary disease)
	Severe dementia (OMC < 18)
	Inability to read and understand Danish written and oral instructions

*Cementless Bi-metric stem® and Exceed ABT Ringloc-x Shell™; OMC= Orientation-Memory-Concentration Test

In total, 499 patients aged 45-70 years were screened in the period May 2012 to May 2014, Figure 6. According to the inclusion criteria 151 patients were not eligible, primarily because they were diagnosed with conditions other than primary OA. Of the remaining 348 patients, 208 patients were excluded due to comorbidity. Over half of them had a prior total joint arthroplasty. The remaining 140 patients were eligible, but 60 patients were not included either because they did not want to participate or because, by mistake, they were not asked.

We performed dropout analyses of differences in the demographic outcomes between patients included in the study and those who did not want to participate or were not asked to participate. We found a higher proportion of patients with the American Society of Anaesthesiology Classification (ASA) score 2 and more females in the not included group, Table 4. The exclusion of this otherwise eligible group of patients may have reduced the external validity of the study.

Table 4. Demographic differences between included and not included patients in the trial

	Included patients (n=77)	Not included patients [#] (n=60)
Male, n (%)*	52 (68)	30 (50)
Age at surgery, mean ± SD	60.9 ± 6.5	62.0 ± 6.6
BMI (kg/m²), mean ± SD	27.3 ± 3.5	27.5 ± 3.3
ASA class; 1: n (%)*; 2: n (%)*; 3 n (%)	58 (75); 13 (17); 6 (8)	27 (45); 30 (50); 3 (5)

ASA= American Society of Anaesthesiology Classification; *Significant difference (Chi-square test)

[#]Not included patients are those who declined to participate or, by a mistake, were not asked to participate

Implication of Study 1

The selected group of patients included in this study constituted younger patients with primary hip OA scheduled for a THA with little or no comorbidity. They provided a homogenous patient group with high internal validity. Nevertheless, performing correlation analyses in a homogeneous group may reduce the strength of the correlation due to limited variance in the study group.

Implications of Study 2 and Study 3

The exclusion criteria Table 3 were primary selected to improve the strength of the results from the gait analyses. Comorbidity in terms of for example, earlier surgery in lower limbs or additional symptomatic joints diseased with OA, may have influenced the outcomes achieved from the gait analyses, hence masking the effect of unilateral hip OA disease and subsequent THA intervention. High BMI reduces a precise marker placement and may also increase the risk of soft tissue artefacts.

Therefore generalisation beyond the study population may be limited but this is an inherent consequence of the RCT design [92]. This trial included younger patients (45 to 70 years) receiving a cementless THA. On the other hand, 80% of all THA patients are diagnosed with primary OA [11] and thus patients in this trial represent the vast majority of all THA patients.

The same considerations must be applied to the study population in Study 3, which constituted a subgroup of all patients included. The selection of patients to participate in the gait analysis study was incorporated into the primary randomisation and no patients declined to participate or withdraw their consent because of the additional amount of visits to the gait

laboratory. No visits were cancelled except for those who were unable to participate due to recent peri-prosthetic or pelvic fractures Figure 9.

Reference group

A convenience sample of 20 healthy able-bodied adults aged 45 to 70 years was recruited to provide a reference data set collected in our own laboratory. The calculation of the GDI was based on this data set and used in Studies 1 and 3. The reference group was recruited using the same inclusion criterion with respect to age and by the same exclusion criteria as the patients, but they were not matched at a group level. The reference group characteristics are shown in Table 5. We did not perform any analyses between the patients and the reference group, since it was not considered an actual control group and the purpose with the studies was not to investigate differences between healthy and patients receiving a THA, but solely to investigate differences between the two interventions. The collection of a reference group data set in our own gait laboratory improves the reliability of the GDI. Thus we avoided introducing bias in the data due to systematic and unknown differences between the gait laboratory protocols [95] and we avoided comparison with typically developing children's gait with that of hip OA/THA patients [64].

Table 5. Demographic characteristics of able-bodied participants in the study

Characteristics	Able-bodied (n=20)
Age (years), mean \pm SD	56.9 \pm 7.1
Male (%)	9 (45)
BMI (kg/m ²), mean \pm SD	25.6 \pm 2.9
Self-selected walking speed (m/s), mean \pm SD	1.33 \pm 0.14

Ethics

The trial complied with the Declaration of Helsinki. It was approved by the Danish Data Protection Agency and The Danish Regional Committee on Biomedical Research Ethics (Southern Denmark), Project-ID S-20120009. A written and orally informed consent was collected from the patients prior to inclusion.

Intervention set-up

All patients had surgery at Odense University Hospital and participated in the same standardised rehabilitation and pain management program. Details about the post-operative medical treatment and rehabilitation can be found in the published protocol [94].

Templating was performed using the software TraumaCad® as part of the pre-operative planning, thus estimating the size and position of prostheses implants aimed at restoring an equal leg length and the femoral off-set. All the surgeons aimed at placing the cup within 5° to 15° of anteversion and 30° to 50° of inclination [96].

During surgery, patients were positioned in the lateral decubitus position. All patients received the same type of cementless components (Bi-metric stem® and Exceed ABT Ringloc-x Shell™ and metal head size 32mm or 36mm).

Posterior approach

PA was performed through an incision over the posterior part of the greater trochanter through the fascia, followed by blunt dissection of the gluteus maximus. Then detachment of the external rotators and incision of the hip capsule was performed [97]. The hip was dislocated by internal rotation and flexion. During closure of the wound, capsular repair and re-insertion of the external rotators were performed if possible.

Lateral approach

LA was performed through a midline incision over the greater trochanter and involved detachment of the anterior one-third of the gluteus medius insertion and gluteus minimus insertion on the tip of the greater trochanter. Excision of the hip capsule was performed on the anterior side of the joint, from the basis of collum femoris to the acetabular rim. The hip was dislocated by external rotation, adduction and flexion. During closure of the wound, re-insertion of the detached part of muscle gluteus medius and minimus was performed. No capsular repair was performed [37].

Two teams of three experienced surgeons performed all operations: one team was responsible for the PA procedure and the other team was responsible for the LA procedure. The surgeons in each team were selected due to their special skills in performing either PA or LA. As a result, we avoided a potential learning curve period and by including three surgeons

in each team, we avoided the potential bias of comparing two surgeons' skills or preference rather than the effect of the surgical approaches.

Outcomes

The outcomes in this thesis were selected on the basis of the recommendation from the Outcome Measures in Rheumatology Clinical Trials (OMERACT) [98] and they involved three of four health dimensions included in the International Classification of Functioning, Disability and Health core sets for osteoarthritis; namely 'body structure', 'body function' and 'activities and participation' [99]. Since the main hypothesis in this thesis was the potential reduction in physical function caused by LA compared with PA, several patient-reported physical function outcomes were selected covering different aspects of this construct. Before choosing the outcome measures it is important to gain knowledge about the measurement properties. The outcome measures must be reliable, valid and responsive. We selected outcome measures that have been validated and that are widely used. The questionnaire in full length is attached in [Appendix E](#). Finally, we supplied the patient-reported outcomes with objective measures of gait function and maximal hip muscle strength.

Primary outcome

HOOS-Physical function

The Hip Disability and Osteoarthritis Outcome Score (HOOS) subscale of Physical Function Short form (HOOS-Physical Function) [100] was used as the primary outcome, with the primary endpoint at 12 months post-operatively. It was chosen because it measures the key objective in this trial, namely whether physical function is influenced by the surgical approach. HOOS- Physical Function is an aggregation and shortening of the two original subscales of HOOS-ADL and HOOS-Sport and Recreation [100]. It is designed to optimise the measurement of physical function and at the same time reduce the burden of long questionnaires for the patients [100, 101]. Studies suggest that the subscale of HOOS-ADL and WOMAC physical function consisting of 17 items, include a number of unnecessary items and the range of demands in the items are limited [101-103]. The HOOS- Physical Function subscale includes five items (three from HOOS-ADL and two from HOOS-Sport and Recreation) that cover a wide range of physical functions, from low demand to high demand functions [100]. Each item is scored on a 5-point Likert scale and the score from each item (0-

4) is included in the calculation of the subscale that ranges from 0 (extreme symptoms) to 100 points (no symptoms). The HOOS-Physical Function has shown high internal consistency and responsiveness in THA patients [101]. All items have been translated into Danish [104].

Secondary outcomes

To supplement the primary outcome the subscales HOOS-Pain and HOOS-Quality of Life from HOOS 2.0 were used. As for HOOS-Physical Function each item is scored on a 5-point Likert scale and the score from each item (0-4) is included in the calculation of the subscale that ranges from 0 (extreme symptoms) to 100 points (no symptoms). HOOS 2.0 has shown high validity, reliability and responsiveness in patients diagnosed with hip OA [105]. The patients completed the Danish version of the questionnaire, that has been validated for trans-cultural adaptation [104].

UCLA

We used a Danish version of the original University of California Los Angeles activity score (UCLA) [106] to measure the patient-reported activity level. It is a questionnaire that evaluate the physical activity on an ordinal 10-point (1-10) Likert scale ranging from 'wholly inactive: dependent on others, and cannot leave residence' to 'regularly participate in impact sports or heavy labour', a higher score being better [106]. It contributes with qualitative information about the clinical outcome after THA [107] and has shown good test-retest reliability, good construct validity, low ceiling effect and to be feasible in the evaluation of THA patients [108, 109].

EQ-5D-3L

The Danish version of the questionnaire [110] EuroQol 5-Dimension 3-Likert scale Health Questionnaire (EQ-5D-3L) [111] was used as a generic health questionnaire. The first part evaluates health status in five dimensions. The global health status index ranges from -0.624 (worst) to 1.00 (best) based on the Danish value set [112]. The second part evaluates the patient's current perception of their overall state of health and is scored on a 'thermometer-like' 100-point visual analogue scale from 0 (worst imaginable) to 100 (best imaginable). We included this questionnaire to evaluate the improvement in the patients overall health status and the results can be interpreted as a global assessment their state of health. However, it cannot be used as a global assessment anchor question. It is recommended to evaluate health

related quality of life (HRQoL) with EQ-5D-3L in THA patients [113] and since 2002, the EQ-5D has been used in the Swedish Hip Arthroplasty Register [114]. The patients completed the Danish version of the questionnaire that has been validated for trans-cultural adaptation [110].

Limping

The cause of limping is probably multifactorial. Poor hip muscle function, and in particular hip abductor muscle weakness, is suggested to cause limping gait [46]. Reduced abductor muscle strength may be caused by the surgical trauma to the hip abductors, changes in the biomechanical properties of the hip joint like the femoral off-set [87, 115] or nerve injury to the gluteus superior nerve [116, 117]. Pain or leg length discrepancy may also lead to limping gait.

To measure the patients' own perception of gait function, we included a question about limping from the function domain of the HHS [118]. Limping is scored on an ordinal 4-point Likert scale (1= no limping, 2= slight, 3= moderate and 4= severe limping). We did not attempt to define limping gait for the patients.

The validity of this isolated domain of the HHS has not been established. However, the reliability and validity of the complete HHS has been tested in a THA population and showed good test-retest and inter-observer reliability, high internal consistency in each domain, low floor effect but high ceiling effect [119]. HHS has been translated into Danish.

Ceiling effect

Despite the careful considerations about choices of PROMs and their measurement properties, we observed a ceiling effect (up to 51% of the patients reached the maximum score) in all the PROMs except for UCLA activity score post-operatively. Pre-operative data showed no signs of a ceiling effect, Table 6. A ceiling effect of 15% is considered the maximum acceptable threshold [120], although, some argue that higher ceiling effects may be acceptable given it is only present post-operatively [121]. A ceiling effect leads to a limitation in the discriminative ability of the questionnaire to detect clinically relevant changes in people who score high on the scale, which is a well-known disadvantage of these PROMs [121, 122]. In this trial, the ceiling effect may be because the study population constituted younger patients with primary hip OA and little or no comorbidity. Consequently, we cannot rule out that some patients

would have improved even more if the HOOS questionnaire had included items with higher physical demands, thus potentially changing the results. However, the absence of a ceiling effect pre-operatively enabled patients to improve in all outcomes.

Table 6. Ceiling effect in the primary and secondary outcomes pre-operatively and post-operatively

Outcomes n (%)	Pre-operatively		12 months follow-up	
	Lateral approach (n=37)	Posterior approach (n=39)	Lateral approach (n=37)	Posterior approach (n=39)
HOOS- Physical Function	0 (0)	0 (0)	15 (41)	20 (51)
HOOS-Pain	0 (0)	0 (0)	16 (43)	18 (46)
HOOS-QOL	0 (0)	0 (0)	9 (24)	13 (33)
EQ-5D-3L-index	0 (0)	0 (0)	20 (54)	23 (59)
EQ-5D-VAS	0 (0)	1 (3)	4 (11)	7 (18)
UCLA Activity score	1 (3)	0 (0)	5 (14)	2 (5)
Limping score	0 (0)	0 (0)	17 (46)	25 (64)

Digital scanning

All questionnaires were printed in a lay-out suitable for digital scanning reducing typing errors [123]. We performed manual data validation where missing data occurred. Ambiguous answers in the UCLA activity score where 2 or more boxes were ticked, the answer which indicated the best activity level was chosen. No ambiguous answers in the Limping score occurred. The HOOS scores were calculated according to the guidelines of HOOS 2.0 [124]. The EQ-5D was calculated according to the User Guide of EQ-5D with the Danish value set [125]. Collectively these procedures almost eliminated missing data in our data set.

Explorative outcomes

GDI

In our gait laboratory we performed 3-DGA using an eight-camera motion capture system (Vicon Motion Systems® Ltd, T40, Oxford, UK), and the Plug-in-Gait marker model, Figure 4. The data were processed in Nexus 1.8 software. Only variables from the affected limb were included in the analyses in Studies 1 and 3.

Figure 4. Plug-in-Gait marker model



As outlined in the introduction, the use of the GDI was applied to evaluate the overall gait deviation from the gait of healthy people throughout the entire gait cycle and thus to evaluate the gait 'quality'. It has been shown that the pre-operative GDI is a predictor for postoperative gait function following THA [65, 66].

In general, gait indices are used to evaluate the overall gait pattern by the deviations from normal gait and at the same time to avoid arbitrary or biased selection of gait variables. The GDI facilitates an objective evaluation and quantification of the deviation from the normal gait pattern. In this thesis, we defined the GDI as a measure of gait 'quality' as also proposed by Cimolin et al. 2014 and Jensen et al. 2015 [65, 126]. The GDI has been validated in children and adults with cerebral palsy [67, 70], but not in hip OA patients.

Despite the obvious advantages of simplicity and evaluation of gait throughout the entire gait cycle, there are limitations. GDI may not include all relevant variables, for example the kinematics of the trunk and kinetics are not included in the Index. GDI only describes how (kinematics) the gait pattern is, but not the underlying cause (kinetics) of the gait pattern [126]. Furthermore, the GDI is a composite gait index, which precludes the possibility of evaluating which variables contribute (positively or negatively) to the sum of the GDI and

therefore the GDI provides no insight into where and in which direction the deviations from normal gait may be [126].

Speed control

Walking speed is known to affect the kinematics during gait [127]. At the pre-operative visit patients were instructed to walk barefooted at a self-selected speed. At the follow-up assessments we collected data from the self-selected speed and from additional trials matching the pre-operative speed ($\pm 5\%$) if patients walked more than 5% faster or slower. This approach enabled analyses of the GDI at a pre-operative controlled walking speed, thus adjusting for the eventual effect walking speed may have on the GDI. No speed-controlled trials were collected in the reference group.

Temporo-spatial parameters and kinematic variables

Temporo-spatial parameters and range of motion (ROM) kinematic variables from hip and knee were also evaluated to supplement the investigation of gait function between the two treatment groups. The outcomes were pragmatically selected, based on which temporo-spatial parameters are commonly reported (walking speed, cadence, double and single support time, and stride length) and ROM kinematic variables from the hip in all three planes and the knee in the sagittal plane [55]. The kinematics from these planes are all included in the GDI.

If we had investigated the kinetics of the hip during gait, we could have further explored the relationship between hip moments as a surrogate measure of hip muscle strength during walking and the maximal hip muscle strength. However, we maintained the focus on the gait function investigated with kinematic variables as decided a priori [94].

In this thesis we used the following definition: The term gait 'quality' was measured by the GDI and described the patient's deviations from non-pathological gait, whereas the term 'gait function' was used in a broader context where the gait was investigated with the GDI, temporo-spatial parameters and kinematic variables.

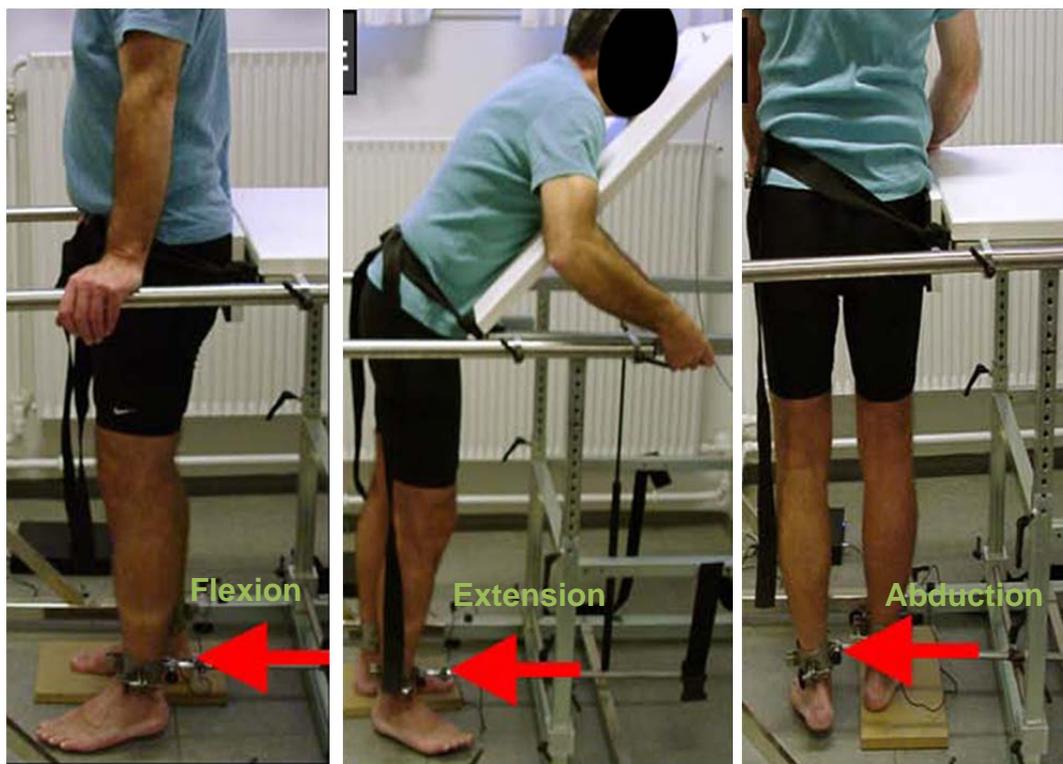
Muscle strength

We measured the maximal isometric hip muscle strength since it may be directly influenced by the two treatments. During LA, the hip abductor muscles are detached and during the PA

the small external rotators and the gluteus maximus are dissected. Thus, the surgically induced trauma may have a direct influence on the hip muscle strength post-operatively- especially hip in abduction [46, 82].

Isometric maximal voluntary contractions (iMVC) in hip abduction, hip flexion and hip extension were recorded in an upright standing position, according to the protocol described by Jensen et al. 2011 [128], Figure 5. Three maximal contractions were performed after one submaximal test contraction in each muscle group to ensure familiarisation. The participants received both visual feedback on a pc-monitor (in the form of a graphical plot of the force over time) and verbal feedback during each test contraction.

Figure 5. The test set-up for measuring maximal isometric hip muscle strength



Reproduced with kind permission of Jensen et al. 2011

For each patient two dice randomisations were used to determine first, the starting limb and second, the sequence of muscle group to be tested. The sequence determined at the first visit was used during all follow-ups. This was done to avoid a systematic learning bias by always starting with the healthy limb and with the same muscle group to be tested.

The two data collectors together performed a visual inspection (face validity) of the contraction curves to ensure there was no pretension, using a custom-made MATLAB® program (MathWorks, Natick, MA, US). The contraction with the highest peak moment (Nm) was selected and normalised according to body mass (Nm/kg). Only iMVC performed on the affected limb were included in the analyses in Studies 1 and 3. iMVC in the standing position has shown acceptable validity [129] and high test-retest reliability in healthy adults and patients with THA [128, 129].

However, the standing position only represents the position of the joint at one time point in the gait cycle. An alternative could have been to use measurement of isokinetic hip muscle strength in a dynamic setup mimicking the range of motion and force-velocity during gait which may have allowed the analysis to reflect a more functional model.

Pain measurement in relation to gait function and hip muscle strength

Pain was measured during all sessions in the gait laboratory: before walking, after walking and after the last iMVC. Pain measurement was important to obtain both in relation to gait and iMVC since pain may influence both gait function and the patient's effort in reaching maximal muscle strength [130, 131]. No analyses adjusted for pain were planned, but the measurements should supply information regarding under which conditions the 3-DGA and muscle strength tests were performed. The validated Numeric Rating Scale for Pain (NRS) ranging from 0= 'no pain' to 10= 'the worst possible pain' was used [132].

Primary endpoint

The greatest improvement in PROs occurs within the first three to six months post-operatively and improvement continues up to the first year [133]. Studies with longer follow-up have shown that no significant improvement is seen beyond the first year [29, 134], which is why prolonging the follow-up period would not add substantially more information about the improvement after treatment. Therefore patients were followed up to 12 months post-operatively. The inclusion of repeated measurements pre-operatively, 3, 6 and 12 months for Study 2 and pre-operatively, 3 and 12 months for Study 3 improves the strength of the studies by reducing the variation in the outcomes and enables a description of the effect of treatment over time [135].

Sample size

The sample size calculation performed prior to Study 2 was based on a repeated measure design [135]. A repeated measure design reduces the number of patients burdened by participating in medical experiments, the time spent on patient recruitment and cost and work related to keeping track of patients. Sample size calculation was performed on the primary outcome HOOS-Physical Function using one pre-operative and three follow-up assessment time-points and an estimated correlation between follow-up measurements of 0.5. A standard deviation of 16.7 pre-operatively and 16.1 post-operatively was used [101]. The minimal clinically important difference (MCID) between treatment groups was *a priori* set to 10 points at 12 months follow-up. Determination of MCID is a difficult task which has great influence on the sample size. We used 10 points on the HOOS-Physical Function scale as recommended by the research group who developed the HOOS questionnaire [124]. In addition 10 points between-group difference has been used in several other recent RCTs involving patients with hip/knee OA and/or total hip/knee arthroplasty [136-138]. In the discussion section, page 59, this issue will be returned to in relation to the results and the existing literature.

The sample size calculation was performed using the 'change-scores' method described by Frison and Pocock 1992 [139] and the function 'sampsimethod (change)' supported by the Stata 13 software. To achieve power of 80% ($\beta = 0.80$) and to detect statistical significant differences at $\alpha = 0.05$, $n = 29$ was needed in each treatment group. To account for possible drop-outs $n = 40$ was recruited. A few patients (2 in the PA group and 1 in the LA group) were lost to follow-up due to withdrawal of consent prior to surgery.

A secondary sample size calculation was conducted to estimate the number of patients needed in Study 3. We based the sample size on the GDI-scores –the *a priori*-defined primary explorative outcome [94]. The MCID for the GDI was *a priori* set to be 7.5 points, which corresponds to half the standard deviation reported in a published RCT using the GDI [67]. The pre-operative standard deviation for the affected limb, in the first 20 patients, was 9 points [140]. To achieve power of 80% ($\beta = 0.80$) and to detect statistically significant differences at $\alpha = 0.05$, $n = 17$ was needed in each group. To account for possible drop-outs a sample size of $n = 20$ in each group was needed. However, at the beginning of the study period, several patients included in Study 3 encountered severe deviations from the planned

treatment protocol (specified in the manuscript of Study 3, [Appendix C](#)). In light of this, we decided to continue the recruitment of patients for Study 3 and ended with 47 patients included in total. Thus, per-protocol analyses (including only patients who strictly followed the planned protocol) were performed on data from 41 patients.

Statistical analysis

The descriptions of the statistics used in this thesis are found in each paper (1-3). No statistical tests were applied to analyse difference in pre-operative patient characteristics or pre-operative outcome values between treatment groups which is in accordance with the CONSORT Statement [92]. Testing the probability that any observed pre-operative between-group differences in randomised groups could have occurred by chance is redundant, since any differences must be caused by chance due to randomisation.

Study 1- correlation

We employed the Pearson's correlation analysis to investigate associations between the GDI as the continuous dependent variable and several independent values (PROs and hip muscle strength in abduction, flexion and extension). The correlation coefficient provides information on the strength of association and direction (positive or negative). Pearson's correlation is suitable when both the dependent and independent variable are continuous and the residuals are normally distributed. The Spearman's correlation was used to analyse the correlation between the GDI and pain measured on the ordinal NRS pain scale (categorical outcome). Multiple linear regression analysis was employed to adjust for walking speed, which is a known confounder of kinematic outcomes [127].

Studies 2 and 3

The mixed linear model analysis with repeated measures and point estimates [141] was used to evaluate the main hypotheses in the RCT: the treatment effect with PA was superior to LA with respect to improvements in PROs, gait function and hip muscle strength after 12 months. This model includes the interaction between treatment and follow-up time, adjusted for pre-operative values and assuming that data are missing completely at random (MCAR) [141]. This statistical analysis model has become more popular within recent years because of advantages over e.g. repeated measures ANOVA [142]. It has the ability to evaluate longitudinal data even if missing data occur during follow-up [142]. However, missing data

were almost absent in both the PROM data set in Study 2 and the explorative 3-DGA data collected in Study 3. Few patients had missing PRO data pre-operatively. To keep these patients within the analyses, data imputation was performed pre-operatively by imputing the mean or median pre-operative value for all the other patients of the relevant outcomes (applied to 3 patients: 2 UCLA activity scores and 1 EQ-5D-VAS). Otherwise, no data imputations were performed in Study 2 and no data imputation was performed at any time in Study 3. We performed the primary analyses using intention-to-treat (ITT) followed by a per-protocol analysis.

The UCLA Activity Score and limping score were *a priori* considered as ordinal data and treated accordingly. But, because of the limited sample size and many categories in each outcome we modelled UCLA Activity Score and limping score as numerical data and used the mixed linear model analysis as described above. Since the analyses of improvement in UCLA Activity Score and limping score were conducted using a linear regression model on ordinal data, these results must be interpreted with some caution.

Describing the difference between the two treatment groups by mean and confidence interval provides information about how precise the estimate of the mean is and the p-value describes the probability that a difference of at least the same size would occur by chance. However, none of these methods provides information about the size of the difference. Hence we reported the Cohen's *d* effect size. Cohen's *d* effect size describes how many standard deviations two group means are apart and is calculated by:

$$d = \frac{\bar{X}_{Group1} - \bar{X}_{Group2}}{SD_{average}}$$

Cohen 1992 defined the medium effect size as: 'an effect likely to be visible to the naked eye of a careful observer'. He defined a small effect size 'to be noticeably smaller than medium but not so small as to be trivial' and the large effect size were describes as 'to be the same distance above the medium as small was below' [143]. In this thesis we used the following definition: An effect size of ≥ 0.2 to < 0.5 , ≥ 0.5 to < 0.8 and ≥ 0.8 was defined as small, medium and large, respectively [143].

The statistical analyses were performed using Stata 13.1 (Stata Corp LP, Brownsville, TX, US).

Numbers Needed to Treat

To calculate the number needed to treat (NNT), the data needed to be dichotomised, establishing a cut point above which the outcome was considered acceptable [144]. The NNT estimates how many patients need to be treated with the superior treatment (hypothesised to be PA) for one more patient to benefit compared with the control treatment (hypothesised to be LA). We dichotomised the data based on a patient acceptable symptom state (PASS) defined as > 88 points on the HOOS-Physical Function subscale as suggested by Paulsen et al. 2014 [145]. We used the Graphpad.com (GraphPad Software Inc, La Jolla, CA, USA) [146] as statistical software. We found the PASS based on HOOS-Physical Function to be relevant to use in this study, since it represents a cut-point for the primary outcome score found acceptable to patients.

Finally, to evaluate the within-group treatment effect we used the minimal clinically important improvement (MCII) defined as the minimal improvement that represents a clinically important improvement from the patient's perspective. Thus, the MCII can also be used to evaluate improvements on an individual level. We used an improvement of >23 points 12 months post-operatively on the HOOS-Physical Function subscale in accordance with Paulsen et al. 2014 [145].

Summary of results

Study 1

Forty-seven patients with unilateral hip-OA and twenty able-bodied participants completed the evaluation with 3-DGA and hip muscle iMVC. The patient group included 34 males and 13 females. They had a mean age of 61.1 ± 6.7 years and a mean BMI of 27.3 ± 3.4 (kg/m²). The patients' characteristics are summarised in Table 7.

Table 7. Characteristics of the hip OA patients included in 3-DGA studies

Characteristics	Hip OA patients (n=47)
Age (years), mean (SD)	61.1 (6.7)
Male (%)	34 (72)
BMI (kg/m ²), mean (SD)	27.3 (3.4)
Self-selected walking speed (m/s), mean (SD)	1.12 (0.18)
Affected side (Right)	25

Hip OA patients had moderately decreased mGDI scores on the affected limb compared to the reference group (87.9 ± 9.1 vs. 100, $p < 0.01$).

Results from the unadjusted and adjusted associations between the mGDI scores and the independent clinical outcomes are summarised in Table 8. Significant, moderate associations between the mGDI and hip abduction iMVC ($R^2 = 0.16$; $p < 0.01$), patient-reported physical function and quality of life ($R^2 = 0.17$; $p < 0.01$ and $R^2 = 0.17$; $p < 0.01$, respectively) were found as well as a moderately significant negative association between mGDI and pain measured with NRS immediately after walking ($R^2 = 0.20$; $p < 0.01$), Table 8.

We observed a significant weak association between hip flexion muscle strength and mGDI ($R^2 = 0.13$; $p = 0.01$). But we found no association between the mGDI and hip extension muscle strength and HOOS-Pain ($R^2 = 0.03$; $p = 0.23$). Adjusting for walking speed did not change the significance of the association, Table 8.

Table 8. Associations between the mGDI as the dependent variable and hip muscle strength, pain and HOOS-scores as independent variables from the OA-affected limb.

Independent outcome variables	Simple association*			Adjusted association**		
	<i>r</i> -value	<i>R</i> ²	<i>P</i> -value	<i>r</i> -value	<i>R</i> ²	<i>P</i> -value
Hip Extension	0.10	0.01	0.50	0.33	0.11	0.08
Hip Flexion	0.37	0.13	0.01	0.41	0.17	0.02
Hip Abduction	0.40	0.16	<0.01	0.43	0.19	0.01
NRS after walk	-0.45	0.20	<0.01	-0.48	0.23	<0.01
HOOS-Physical Function	0.41	0.17	<0.01	0.45	0.20	<0.01
HOOS-Pain	0.18	0.03	0.23	0.35	0.12	0.06
HOOS-Quality Of Life	0.41	0.17	<0.01	0.50	0.25	<0.01

* Continuous data analysed with Pearson's correlation and ordinal data analysed with Spearman's correlation

** Multiple linear regressions adjusting for walking speed

Abbreviations: OA= Osteoarthritis; GDI= gait deviation index; NRS=Numeric Rating Scale for pain; HOOS= Hip disability and Osteoarthritis Outcome Score.

Study 2

Eighty patients were randomised and 77 and 69 patients were available for ITT and per-protocol analyses, respectively, Figure 6.

Eight (10%) patients (3 in the LA group and 5 in the PA group) did not follow the protocol for various reasons, Figure 6.

Pre-operative patient characteristics and surgical-related outcomes are presented in Table 9. There was no difference between the treatment groups regarding femoral head size. But more patients in the LA group received a lateralised stem and the LA procedure had a longer duration of surgery.

Within-group and between-group improvements in patient-reported outcomes

Within-group and between-group change scores are presented in Table 10. We found a statistically non-significant difference in the mean change score of HOOS-Physical Function of -3.3 [95% CI: -8.7 to 2.1]. Thus, the improvement in physical function 12 months post-operatively following PA treatment was not superior to the improvement following LA treatment. The same applied to all the earlier time-points,

Figure 7. Furthermore, there was no additional improvement in the PA group compared with the LA group in the secondary outcomes at 12 months (HOOS-Pain, HOOS-QOL, UCLA Activity Score, EQ-5D-3L and EQ-5D-VAS), except for limping, where we found a significant difference in improvement of 0.4 [95% CI: 0.05 to 0.66] point on the 4-point Likert scale in favour of PA, Figure 8 and Table 10.

Figure 6. Flow of patients included in the trial evaluating patient-reported outcomes

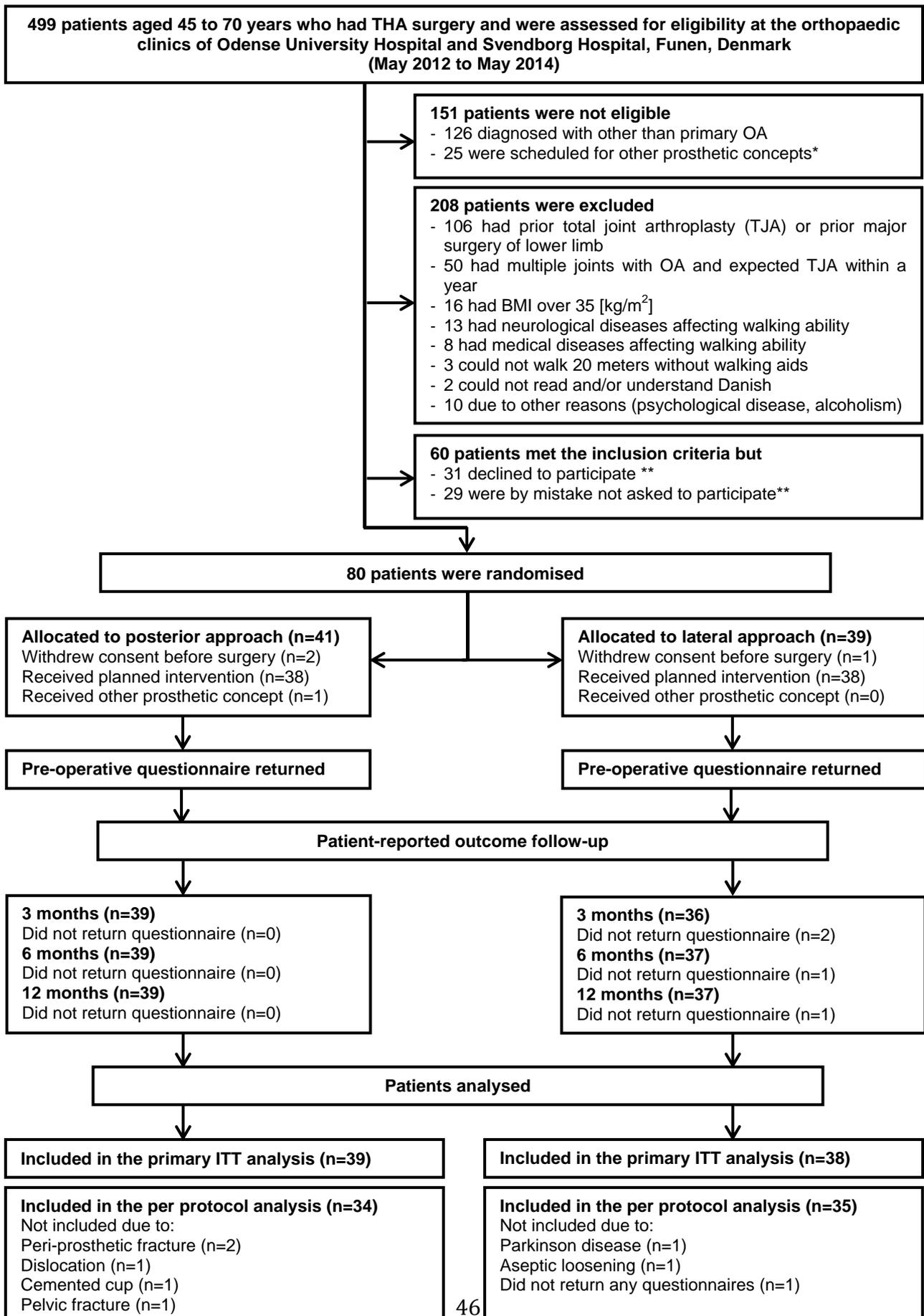


Table 9. Demographic and clinical characteristics for all patients in each treatment group

	Lateral Approach (n=38)	Posterior Approach (n=39)
Demographic patient characteristic		
Male, n (%)	26 (68)	26 (67)
Age at surgery, mean \pm SD	60.2 \pm 6.9	61.5 \pm 6.1
BMI (kg/m ²), mean \pm SD	27.0 \pm 3.4	27.7 \pm 3.6
Affected side, right (%)	20 (53)	19(49)
ASA class; 1: n (%); 2; n (%); 3 n (%)	28 (74) ; 7 (18); 3 (8)	30 (77); 6 (15); 3 (8)
OMC score, mean \pm SD	26.6 \pm 2.1	26.2 \pm 2.4
Clinical characteristics		
Pre-operative Hgb (mmol/L), mean \pm SD	9.1 \pm 0.8	8.9 \pm 0.6
Post-operative Hgb (mmol/L), mean \pm SD	6.9 \pm 1.2	6.9 \pm 0.9
Blood loss (ml), mean \pm SD	363 \pm 171	362 \pm 140
Received blood transfusion, n (%)	2 (5)	1 (3)
Anaesthesia, n (%)		
Spinal	32 (84)	26 (67)
General	6 (16)	13 (33)
Duration of surgery (min), mean \pm SD*	60.4 \pm 12.3	53.7 \pm 12.6
Prosthetic head size, n (%)		
32mm	30 (79)	33 (85)
36 mm	8 (21)	6 (15)
Stem type, n (%)**		
Standard	8 (21)	19 (49)
Lateralised	30 (79)	20 (51)
Patient-reported outcome measures		
HOOS-Physical Function, mean \pm SD	53.1 \pm 14.3	52.8 \pm 17.4
HOOS-Pain, mean \pm SD	43.8 \pm 14.8	42.6 \pm 16.5
HOOS-Quality Of Life, mean \pm SD	28.5 \pm 12.2	28.4 \pm 14.4
EQ-5D-3L, mean \pm SD	0.61 \pm 0.15	0.55 \pm 0.20
EQ-5D-VAS, mean \pm SD	59.5 \pm 17.9	57.0 \pm 24.5
UCLA Activity Score*, median (Q1; Q3)	5 (4;7)	5 (3;6)
Limping Score*, median (Q1; Q3)	3 (3;3)	3 (3;3)

BMI= Body mass index; ASA= American Society of Anaesthesiology Classification; OMC= Orientation–Memory–Concentration Test (0 = worst outcome, 28 = best outcome); Hgb=haemoglobin

*Significant difference between treatment groups tested with Students t-test; or ** tested with the Chi-square test

HOOS= Hip disability and Osteoarthritis Outcome Score (Scores range from 0 to 100 with higher scores indicating better outcome);

EQ-5D-3L= European Quality of Life Health Questionnaire (Scores range from -0.624 to 1.0 with higher scores indicating better outcome);

EQ-5D-VAS= European Quality of Life visual analogue scale of overall state of health (Scores range from 0 to 100 with higher scores indicating better outcome);

UCLA= The University of California Los Angeles Activity Score (Scores range from 1 to 10 with higher scores indicating better outcome);

Limping (Score range from 1= no limping to 4= severe limping);

*Median (Q1; Q3 represent 25th and 75th percentiles) presented for the UCLA score and Limping score.

Table 10. Mean difference in patient-reported outcome scores within and between treatment groups pre-operatively to 12 months follow-up (ITT)

PROMs	Within-group change		Between-group change (LA minus PA) [#]		Cohen's d effect size
	Pre-operative to 12 months follow-up, mean [95% CI]		Pre-operative to 12 months follow-up, mean [95% CI]		12 months follow-up, ES [95% CI]
	Lateral approach (n=37)	Posterior approach (n=39)	(n=77)	p-value	
HOOS-Physical Function	36.0 [30.2 to 41.7]	39.4 [34.5 to 44.3]	-3.3 [-8.7 to 2.1]	0.23	0.25 [-0.2 to 0.7]
HOOS-Pain	46.2 [39.8 to 52.6]	49.5 [44.3 to 54.6]	-2.6 [-8.7 to 3.6]	0.41	0.14 [-0.3 to 0.6]
HOOS-Quality Of Life	50.7 [42.2 to 59.1]	55.6 [49.9 to 61.3]	-4.9 [-13.2 to 3.5]	0.25	0.22 [-0.2 to 0.7]
EQ-5D-3L	0.27 [0.21 to 0.33]	0.34 [0.28 to 0.40]	-0.04 [-0.11 to 0.03]	0.28	0.08 [-0.4 to 0.5]
EQ-5D-VAS	23.6 [15.5 to 31.8]	30.2 [22.5 to 38.0]	-4.6 [-11.7 to 2.5]	0.21	0.22 [-0.2 to 0.7]
	Median (Q1; Q3) [*]				
UCLA Activity Score	1 (0; 3)	2 (1; 3)	-0.6 [-1.3 to 0.0]	0.06	-
Limping Score	-1 (-2; -1)	-2 (-2; -1)	0.4 [0.0 to 0.7]	0.02	-

HOOS= Hip disability and Osteoarthritis Outcome Score (Scores range from 0 to 100 with higher scores indicating better outcome);

EQ-5D-3L= European Quality of Life Health Questionnaire (Scores range from -0.624 to 1.0 with higher scores indicating better outcome);

EQ-5D-VAS= European Quality of Life visual analogue scale of overall state of health (Scores range from 0 to 100 with higher scores indicating better outcome);

UCLA Activity Score = The University of California Los Angeles activity score (Scores range from 1 to 10 with higher scores indicating better outcome);

Limping Score (Score range from 1= no limping to 4= severe limping);

^{*}Median (Q1; Q3 represent 25th and 75th percentiles) presented for UCLA and Limping score in within-group change.

- Cohen's effect size is not calculated due to the ordinal nature of the outcome.

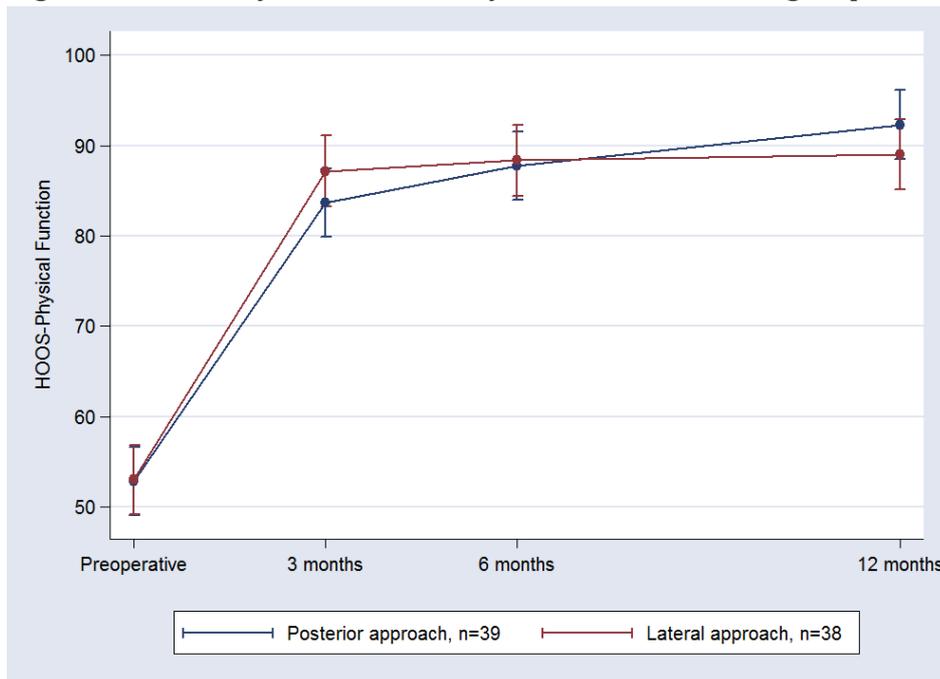
[#]Results from a random effects mixed linear model analysis (repeated measures) with PROM variable as the dependent variable and pre-operative value, treatment, time and interaction between time and treatment as independent variables. Data from all assessment time-points (Pre-operative, 3, 6 and 12 months post-operatively) were used in the model. A numerically positive value indicates a better outcome for LA except for Limping.

Cohen's d effect size for the primary outcome and all secondary outcomes at 12 months were small and non-significant, Table 10.

The per-protocol analysis changed the results on the self-reported limping score to a non-significant improvement in favour of PA. All other results remained unchanged ([Appendix C](#)).

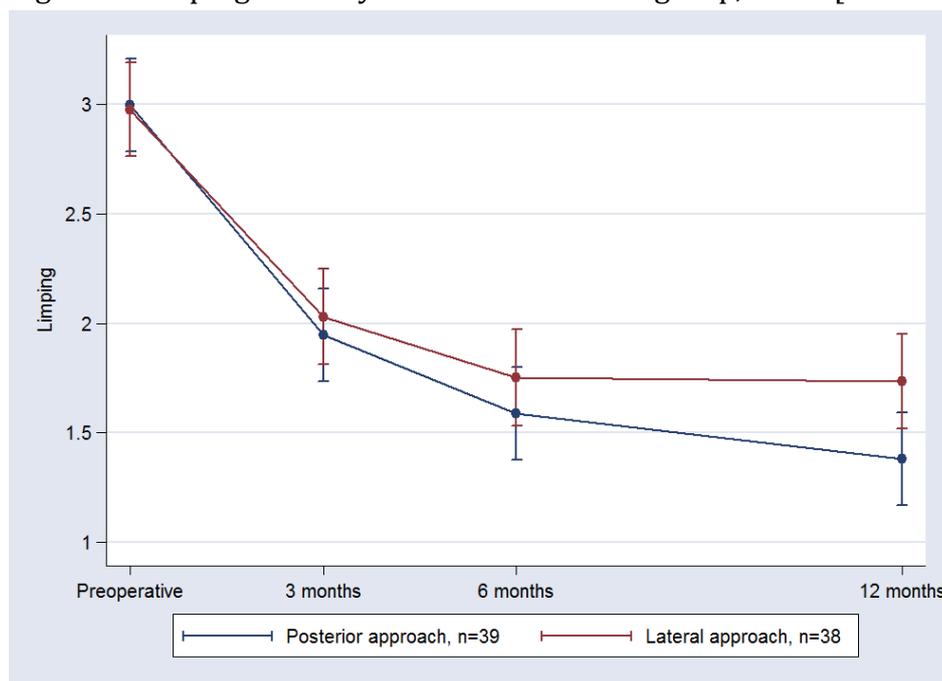
A significant within-group improvement in HOOS-Physical Function was observed in both treatment groups, 39.4 [95% CI: 34.5 to 44.3] and 36.0 [95% CI: 30.2 to 41.7] for PA and LA, respectively. Both treatments improved more than 23 points on the HOOS-Physical Function subscale defined as the MCII. The greatest improvement in all outcomes occurred within the first 3 months, as shown in Figure 7 and Figure 8. On an individual level 8 patients within the LA group did not improve more than 23 points on HOOS-Physical Function subscale compared with 4 patients in the PA group.

Figure 7. HOOS Physical Function by time and treatment group, mean [95% CI]



Scores range from 0 to 100 with higher scores indicating better outcome

Figure 8. Limping Score by time and treatment group, mean [95% CI]



0= 'no limping', 4 = 'severe limping'

Number needed-to-treat analysis

Fourteen (38%) patients in the LA group had a HOOS-Physical Function score below 88 points compared with 12 (31%) in the PA group. The absolute risk reduction was 7% [95% CI: -14.2% to 28.4%] and the NNT was 14 patients, Table 11. This means that one in every 14 patients would benefit from the treatment with PA compared to LA. However, the 95% confidence interval for the absolute risk reduction extends from a negative number (PA may harm) to a positive number (PA may benefit) and therefore we cannot conclude with 95% certainty whether PA is harmful, has no effect, or is helpful, compared with LA.

Table 11. Number needed to treat (NNT) based on the HOOS-Physical Function score

Acceptable Outcome Score for HOOS-Physical Function	Lateral approach (n= 37)	Posterior approach (n= 39)
Yes: HOOS-Physical Function > 88, n (%)	23 (62)	27 (69)
No: HOOS-Physical Function < 88, n (%)	14 (38)	12 (31)

Patient acceptable symptom state (PASS) based upon a cut point of 88 HOOS-Physical Function points 12 months post-operatively
 HOOS= Hip disability and Osteoarthritis Outcome Score (Scores range from 0 to 100 with higher scores indicating better outcome)

Study 3

Inclusion

The flow of patients is presented in Figure 9. Forty-seven patients were allocated to participate in 3-DGA (sub-group analysis). One patient received a cemented cup and was not followed up.

Demographic and clinical characteristics for the patients are presented in Table 12. Pre-operative pain was present in both groups during testing with no differences between the treatment groups.

Table 12. Demographic patient characteristics and pre-operative clinical characteristics for the affected limb

Outcomes	Lateral Approach (n=24)	Posterior Approach (n=23)
Demographic characteristics		
Male, n (%)	17 (71)	17 (74)
Age (years), mean ± SD	60.5 ± 6.6	61.0 ± 6.7
BMI (kg/m ²), mean ± SD	27.3 ± 3.4	27.5 ± 3.8
Affected side; right: n (%)	14 (58)	11 (48)
Operative outcomes		
Anaesthesia, n (%)		
Spinal	20 (83)	15 (65)
General	4 (17)	8 (35)
Gait deviation index (GDI), mean ±SD	88.5 ± 9.0	87.4 ± 9.5
Temporo-spatial variables, mean ± SD		
Self-selected walking speed (m/s)	1.15 ± 0.17	1.10 ± 0.18
Cadence, (steps/min)	114 ± 10	113 ± 10
Double support time (%)	24.3 ± 2.7	24.8 ± 2.6
Single support time (%)	36.8 ± 1.9	36.3 ± 2.0
Stride length (m)	1.22 ± 0.15	1.17 ± 0.16
Dynamic range of motion (degree°), mean ± SD		
Hip sagittal	28.1 ± 7.1	27.9 ± 7.4
Hip frontal	7.2 ± 3.1	6.3 ± 1.9
Hip transversal	19.4 ± 5.0	19.2 ± 3.5
Knee sagittal	51.9 ± 5.4	50.7 ± 6.1
Hip muscle strength, mean ±SD		
Hip Abduction (Nm/kg)	1.6 ± 0.3	1.7 ± 0.4
Hip Flexion (Nm/kg)	1.4 ± 0.4	1.2 ± 0.4
Hip Extension (Nm/kg)	2.4 ± 0.5	2.2 ± 0.6
Numeric Rating Scale for pain (NRS) (0-10), median (Q1; Q3)		
Before 3-DGA	3.5 (2; 5)	3 (2; 6)
After 3-DGA	4.5 (1.5; 6)	5 (2; 7)
After hip muscle strength test	5.5 (3; 7.5)	6 (4; 8)

BMI = Body mass index; NRS: 0 = 'no pain' to 10 = 'worst possible pain'; Median (Q1; Q3 represent 25th and 75th percentiles); 3-DGA= 3-Dimensional Gait Analysis

Pain measured on the NRS for pain was absent in both groups post-operatively. The median NRS score after maximal hip muscle strength at 12 months for LA and PA were: 0 (0; 0) and 0 (0; 0)), respectively, with no difference between the two treatment groups.

Per-protocol-analysis

Six out of 47 (13%) patients did not follow the protocol, Figure 9. We therefore performed a per-protocol-analysis on the 41 patients who strictly followed and completed the protocol.

Within-group and between group improvements in gait function

The mGDI in both groups remained almost constant (\approx 88 points both pre- and post-operatively). Consequently, the improvement in gait 'quality' at 12 months was not superior following PA treatment compared with the LA treatment, Table 13 and Figure 10.

Single and double support time in the affected limb a significant difference in favour of PA was found. However, we found no difference in improvement in walking speed, cadence and stride length between the two groups, Table 13.

Within-group improvements in the PA group were found in most of the variables except for cadence, whereas within-group improvements were not found for cadence, single and double support for the LA group, Table 13.

Dynamic range of motion: No difference in improvement in dynamic range of motion measured during gait was observed between the two treatment groups, Table 13.

Within-group improvement was found in hip sagittal and frontal planes, but not in the hip transversal plane or knee sagittal plane for both groups.

Hip muscle strength

The hip muscle strength in abduction and flexion improved more in the PA group than the LA group at 12 months follow-up. The mean change was: -0.20 [95%CI: -0.4 to 0.0] and -0.20 [95%CI: -0.4 to 0.0], in abduction and flexion, respectively. No between-group difference was found for hip extension muscle strength Table 13.

The per-protocol-analysis enhanced these differences for both muscle groups: -0.25 [95%CI: -0.5 to 0.0] and -0.21 [-0.4 to 0.0] for abduction and flexion, respectively. This was also shown

in the slight increase in the Cohen's *d* effect size for abduction from 0.6 in the ITT analyses to 0.7 in the per-protocol analysis.

In the LA group there was no significant within group improvement in hip abductor strength in the affected limb at 12 months -0.1 [95%CI: -0.3 to 0.1], Figure 11. However, we did find within-group improvements for both treatment groups in hip flexion and extension.

Figure 9. Flow of patients included in the explorative trial evaluating gait function and hip muscle strength

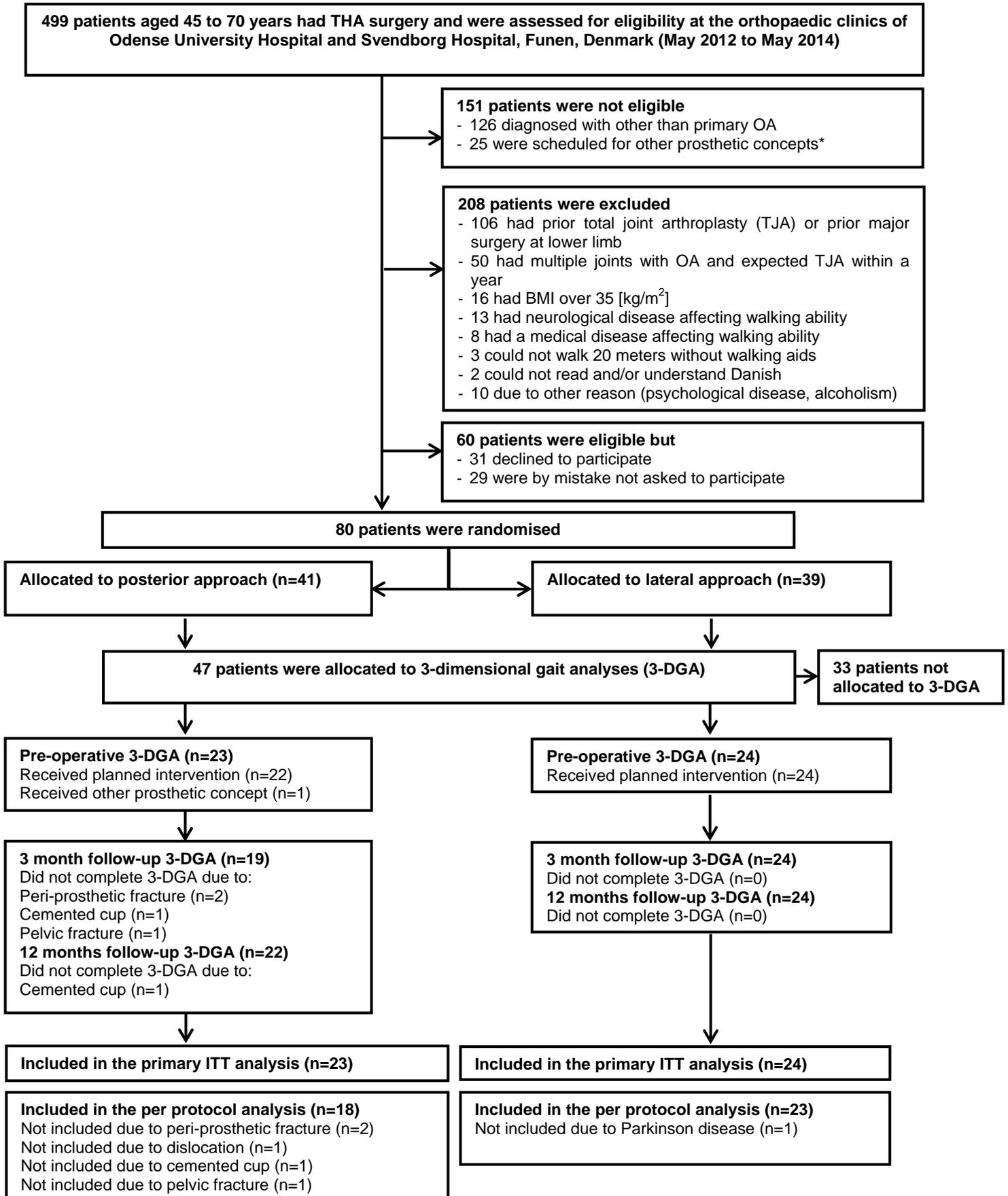


Table 13. Mean change scores within and between treatment groups at 12 months follow-up (Intention to treat analysis)
Gait Deviation Index, temporo-spatial parameters, kinematic variables and hip muscle strength from the affected limb

Outcome	Within-group mean change Pre-operative to 12 months follow-up [95% CI]		Between-group mean change (LA minus PA) [§]	Cohen's <i>d</i> effect size
	Lateral approach <i>n</i> =24	Posterior approach <i>n</i> = 23	Pre-operative to 12 months follow-up [95% CI] <i>n</i> =47	12 months follow-up [95% CI]
Gait Deviation Index (GDI)[#]				
Self-selected walking speed	-0.2 [-5.6 to 5.2]	0.7 [-4.6 to 6.1]	-0.1 [-4.7 to 4.5]	0.0 [-0.6 to 0.6]
Controlled walking speed	-0.2 [-5.7 to 5.4]	-0.7 [-5.9 to 4.5]	1.6 [-3.1 to 5.8]	-0.2 [-0.8 to 0.4]
Temporo-spatial variables				
Self-selected walking speed, (m/s)	0.13 [0.03 to 0.23]*	0.16 [0.05 to 0.26]*	-0.01 [-0.06 to 0.05]	-0.2 [-0.8 to 0.4]
Cadence, (steps/min)	1.0 [-4.8 to 6.8]	2.7 [-2.8 to 8.3]	-1.8 [-4.2 to 0.6]	0.1 [-0.5 to 0.7]
Double support time, (%)	-0.5 [-2.1 to 1.1]	-2.1 [-3.8 to -3.3]*	1.3 [0.3 to 2.4]	-0.3 [-0.9 to 0.3]
Single support time, (%)	0.8 [-0.3 to 2.0]	2.3 [1.2 to 3.5]*	-1.3 [-2.1 to -0.4]	0.5 [-0.1 to 1.1]
Stride length, (m)	0.13 [0.04 to 0.22]*	0.13 [0.04 to 0.23]*	0.02 [-0.02 to 0.06]	-0.3 [-0.9 to 0.3]
Dynamic range of motion (degree°)				
Hip sagittal ROM	12.8 [9.1 to 16.6]*	11.2 [6.7 to 15.8]*	1.8 [-1.1 to 4.7]	-0.3 [-0.9 to 0.3]
Hip frontal ROM	2.6 [0.9 to 4.4]*	2.0 [0.6 to 3.3]*	1.0 [-0.3 to 2.3]	-0.6 [-1.1 to 0.0]
Hip transversal ROM	0.5 [-2.4 to 3.5]	0.1 [-2.5 to 2.7]	0.6 [-1.5 to 2.7]	-0.1 [-0.7 to 0.5]
Knee sagittal ROM	0.5 [-2.5 to 3.4]	1.8 [-1.9 to 5.5]	-1.1 [-3.3 to 1.2]	0.0 [-0.6 to 0.6]
Hip muscle strength (Nm/kg)				
Hip abduction	0.08 [-0.15 to 0.32]	0.30 [0.04 to 0.55]*	-0.20 [-0.4 to 0.0]	0.6 [0.0 to 1.2]
Hip flexion	0.29 [0.05 to 0.54]*	0.57 [0.32 to 0.81]*	-0.20 [-0.4 to 0.0]	0.2 [-0.4 to 0.8]
Hip extension	0.33 [0.03 to 0.63]*	0.49 [0.05 to 0.93]*	-0.07 [-0.3 to 0.2]	0.0 [-0.6 to 0.6]

[§]Results from a random effects mixed linear model analysis (with repeated measures) with absolute value as the dependent variable and pre-operative value, treatment group, time and interaction between time and treatment as covariates. Data from all assessment points (pre-operatively, 3 and 12 months post-operatively) were included in the model.

[#] GDI scores range from 0 to >100 with higher scores indicating near normal walking pattern; GDI= Gait Deviation Index; Nm= Newton meter.

*Significant difference within group, tested with a paired t-test.

Figure 10. Mean score in Gait Deviation Index at a self-selected walking speed by time and treatment group; mean [95% CI]

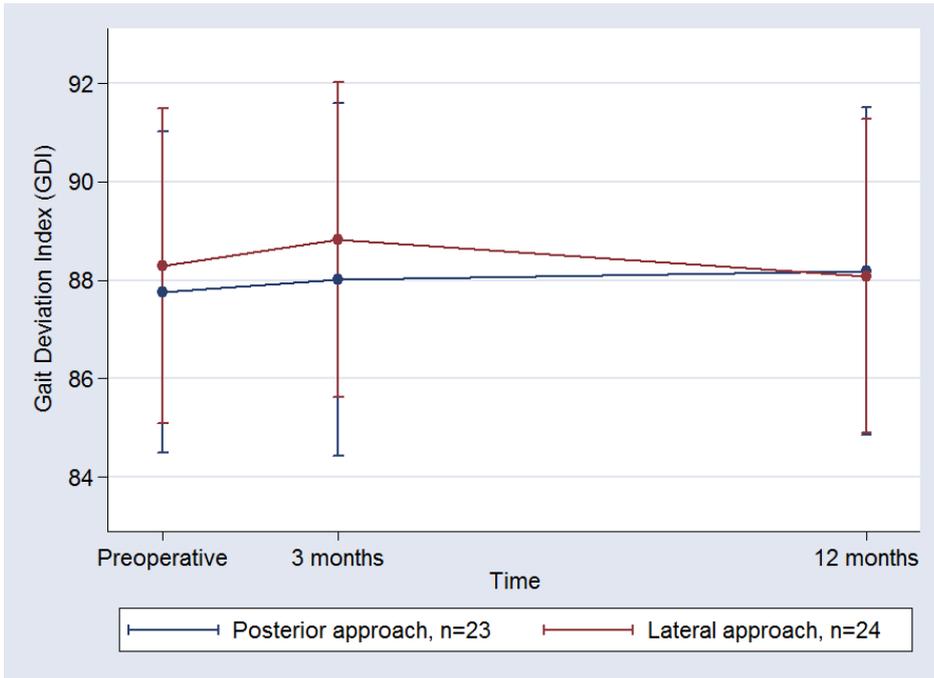
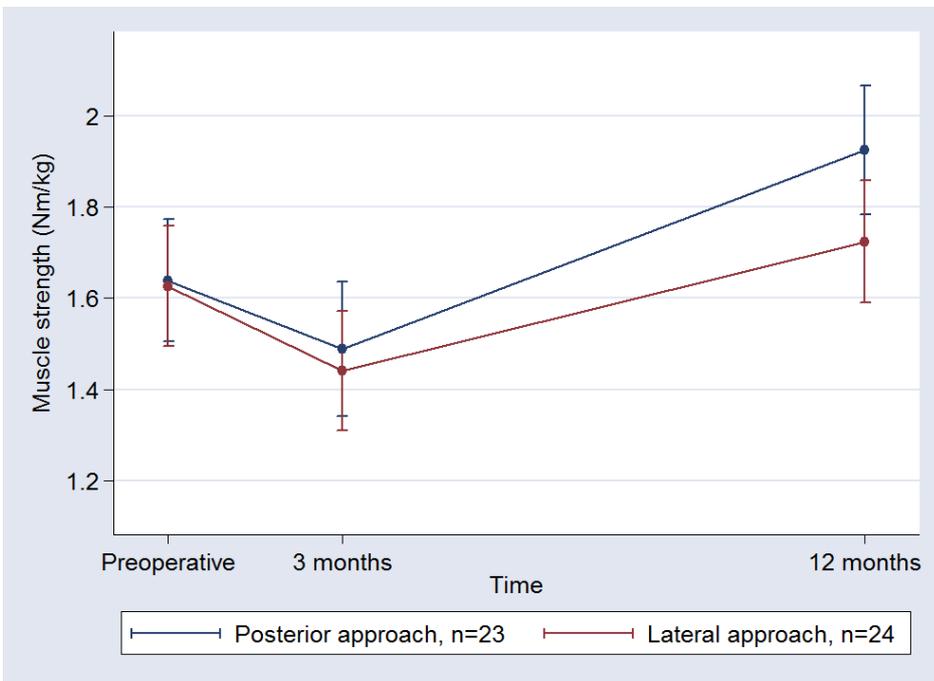


Figure 11. Mean score in maximal hip abduction strength by time and treatment group; mean [95% CI]



Supplementary results

Limping

Post-hoc analyses of the data set were performed, where all 77 patients were divided into two groups depending on their self-reported limping score. All patients with a limping score of 1 = no limping were one group and the remaining patients with a limping score > 1= slight, moderate or severe limping constituted the other group.

Table 14 shows the frequency of patients with limping in the PA group compared with the LA group. There was no significant difference.

Table 14. The proportion of patients with and without self-reported limping in the two treatment groups

Self-reported limping status at 12 months follow-up	Lateral approach (n=37)	Posterior approach (n=39)
No limping, n (%)	17 (46)	25 (64)
Slight to severe limping, n (%)	20 (54)	14 (36)

No significant difference between treatment groups p= 0.11 (The Chi-square test)

The analyses presented in Table 15 were based on the patients grouped irrespective of their original treatment allocation. We evaluated if there were significant difference in the PROMs at 12 months between the group of patients with limping compared with the group without limping. For all PROMs, we found significantly better outcomes for the group of patients without limping.

Table 15. Patient-reported outcomes in patients with and without self-reported limping, irrespective of surgical approach at 12 months follow-up

PROM	No limping [95% CI] (n=42)	Slight to severe limping [95% CI] (n=34)	Mean difference* [95% CI]	p-value
HOOS-Physical Function	95.2 [92.7 to 97.8]	85.2 [80.0 to 90.3]	10.1 [4.8 to 15.4]	<0.00
HOOS-Pain	96.3 [93.7 to 98.9]	84.7 [78.8 to 90.6]	11.6 [5.7 to 17.5]	<0.00
HOOS-QOL	89.0 [84.6 to 93.4]	72.8 [64.4 to 81.2]	16.2 [7.3 to 25.1]	<0.00
EQ-5D-3L-index	0.94 [0.90 to 0.97]	0.82 [0.77 to 0.88]	0.11 [0.05 to 0.18]	<0.00
EQ-5D-VAS	91.8 [88.1 to 95.6]	78.1 [72.6 to 83.6]	13.7 [7.3 to 20.1]	<0.00

*Student's t-test (two-sample t test using groups)

Radiographic measurements of change in off-set

We evaluated the changes in femoral off-set, cup-off-set, total off-set and abductor moment arm in a sub-group of patients (28 patients from each of the LA group and PA group) with a valid set of pre-operative and post-operative radiographs.

Table 16. Change in off-set and abductor moment arm in the two groups at 12 months follow-up

Radiographic measurements	Lateral approach (n=28)	Posterior approach (n=28)	Between-group mean difference (LA-PA)* mean [95% CI], p-value
	Mean ±SD	Mean ± SD	
ΔFO (mm)	0.8 ± 4.4	5.1 ± 6.6	-4.3 [-7.4 to -1.3], < 0.01
ΔCO (mm)	-7.8 ± 3.8	-5.9 ± 4.3	-1.9 [-4.1 to 0.2], 0.08
ΔTO (mm)	-7.1 ± 5.6	-0.8 ± 6.8	-6.3 [-9.6 to -3.0], < 0.00
ΔAM (mm)	-0.7 ± 5.4	4.1 ± 5.2	-4.8 [-7.6 to -1.9], < 0.00

*Tested with Students t-test

Abbreviations: FO=femoral offset, CO=cup offset, TO=total offset, AM=abductor moment arm

We found that patients in the PA group increased more in femoral off-set, total off-set and abductor moment arm compared with the LA group, Table 16. These finding will be discussed below in relation to the difference found in hip muscle strength, Discussion section page 71.

Discussion

Patient-reported outcomes and minimal clinically important difference

The aim in Study 2 was to evaluate the efficacy of PA compared with LA measured with patient-reported physical function, pain, quality of life, physical activity and limping. The results from the current trial provide level I evidence about the superiority of PA compared with LA 12 months post-operatively. Contrary to our hypotheses, no significant difference in improvement of patient-reported physical function was observed. The same applied to all secondary outcomes except for limping score.

Four registry-based studies (three of which were published after initiation of the current trial), one prospective cohort study and one RCT have investigated the difference in PROs between PA and LA previously, Table 17, page 63. All the studies reports statistically significantly better outcome for PA compared with LA except for the RCT study by Witzleb et al. 2009 [51]. Witzleb et al. 2009 found no significant difference between PA and LA at 3 months follow-up measured with the HHS as a surgeon-reported outcome measure and consequently it cannot be considered as a genuine PROM [51]. However, the study did find a non-significant tendency to better outcomes for the patients in the PA group compared with the LA group of 10-15 points on the three subscales measured with WOMAC, thus in line with the results from this and the other studies.

The prospective cohort study by Palan et al. 2009 reported a statistically significant difference in OHS of 2 points after 1 year, but no difference was present at 5 years follow-up [134]. They defined *a priori* a MCID of 2 points based on the work of Murray et al. 2007 [147]. Murray et al. 2007 estimated the MCID to be between 3-5 points, and discussed the possibility that it may be as low as 2 points. Thus, although the study by Palan et al. 2009 found a statistically significantly difference at 1 year, it is questionable whether it has any clinical relevance to patients. Furthermore, the study by Palan et al. 2009 included patients with any indication for THA, also patients with femoral fractures, which constitute a different patient group compared to patients with OA [11, 148] and the findings may also be limited by the heterogeneity of implants used. These factors reduce the internal validity of this study together with the non-randomised design [134]. However, the study by Jameson et al. 2013 supports the findings by Palan et al 2009, as they also found a similar difference of 2 points in

OHS 6 months post-operatively in a primary hip OA cohort [149]. But they did not report longer follow-up time and the difference between groups is less than the MCID.

The results from Study 2 are best compared with the studies by Amlie et al. 2014 and Lindgren et al. 2014, because the same PROMs were applied.

We found a systematic tendency towards higher numeric improvements for the PA group compared with the LA group of 2.6, 3.3 and 4.9 points on the subscales HOOS-Pain, HOOS-Physical Function and HOOS-QOL, respectively, Table 10. These findings align with the registry-based cohort study by Amlie et al. 2014. They investigated 852 THA patients receiving PA or LA, with 1-3 years follow-up. The study showed a significant difference between the two treatments of approximately 4 points on the HOOS-subscale. All differences were in favour of PA [28], but, no baseline data were available and no MCID was defined *a priori*.

One may argue that the current trial did not include sufficient patients and that inclusion of more patients would have turned the 'systematic tendency towards higher numeric improvement' to a significant difference. A post-hoc sample size calculation based on HOOS-Physical Function showed that by inclusion of 183 patients in each treatment group, the difference of 3.3 point in favour of PA would become statistically significant, which is in accordance with earlier studies as outlined above [28, 134, 149]. However, by including more patients and turning the small non-significant difference into a statically significant difference does not make the difference more or less clinically important to patients.

We based the sample size calculation on the HOOS-Physical Function subscale with 10 points as the MCID. Yet, it is not a simple task to determine the MCID, and it probably varies depending on both the patient group and the intervention being evaluated [150, 151]. Our decision was based on published evidence and related RCT studies using the HOOS questionnaire as the primary outcome measure [124, 137, 152-154]. Also, more recent RCTs have been published using a HOOS-subscale as primary outcome and 10 points as the MCID [136, 138, 155]. Therefore, we do not consider a difference of 3.3 points on the HOOS-Physical Function subscale ranging from 0 to 100 to be clinically relevant for patients. And the same applies for the results from the study by Amlie et al. 2014.

The secondary outcomes from Study 2 also showed a systematic tendency towards higher numeric improvements for the PA group in the general health status measured with EQ-5D-3L-index and in EQ-VAS. We found between-group differences of 0.04 and of 4.6, respectively, Table 10. This aligns with findings from the registry-based study of 42,233 THA patients undergoing PA or LA with 6 years follow-up [29]. Lindgren et al. 2014 reported a statistically significant better EQ-5D-index outcome of 0.03 and EQ-VAS of 1.5 in favour of the PA group at 1 year follow-up and the differences were maintained at 6 years follow-up [29]. However, these differences are of small magnitude and not considered above the MCID for EQ-5D [156, 157]. Overall, the estimates of the MCID for EQ-5D range from 0.03, estimated for patients with low back pain, to 0.52 estimated for patients with recurrent lumbar stenosis [156]. One study has reported a MCID of 0.08 for a hip OA population undergoing THA [157]. The authors of the study by Lindgren et al. 2014 did not *a priori* define a MCID, and they also question if the observed difference has any clinical relevance for patients. Furthermore, they discussed the possibility that unknown subgroups among patients in the LA group had more severe problems, hence reducing the overall outcome of EQ-5D, which may also be the case in the current study.

Both patient groups in the current trial exceeded the MCII of 23 points on HOOS-Physical Function subscale [145] shown by the within-group change of 36.0 [30.2 to 41.7] and 39.4 [34.5 to 44.3] points in the LA and PA groups, respectively, Table 10.

The MCII of 23 points can also be used as cut point for evaluation of the individual improvement. In this trial, eight patients in the LA group and four in the PA group did not achieve improvement above 23 points, however in both groups, two of these patients had a pre-operative HOOS-Physical Function score above 80 points and hence they were not able to improve 23 points due to the ceiling effect. The evaluation of MCII is only possible when baseline data are available.

The NNT analysis was based on a PASS value of 88 points on the HOOS-Physical Function subscale [145] and this analysis supports the conclusion that no superiority of the PA versus LA was present, Table 11. The Cohen's *d* effect size also supports this notion as the effect size was small to negligible for all outcomes (range: 0.08 – 0.25), Table 10.

The post-operative mean of HOOS-Physical Function in both treatment groups was higher than the PASS value of 88 points [145].

Collectively, all the studies that have investigated the difference in PROs between PA and LA found small differences in favour of PA. But it is questionable whether these differences constitute any clinically relevant difference based on the available literature regarding MCID.

Table 17. Studies comparing patient-reported outcomes in patients with PA versus LA

Study	Design	Number of patients	Diagnosis	Approach	Follow-up	PROM	Results Mean difference [95% CI]	Dislocations	Limping
Witzleb et al. 2009	RCT	PA: 30 LA: 30	Primary OA	PA with repair LA, Hardinge	3 months	WOMAC subscales	Non-significant difference in improvement of 10-15 points in favour of PA*	Non-significant PA 3.3% LA 0%	Trendelenburg test PA 13% LA 37% Non-significant
Palan et al. 2009	Prospective cohort-study Multicentre Baseline data	PA: 389 LA: 688	All- incl. fractures	PA with repair LA, Hardinge	3 months 1 year 3 years 5 years	OHS	Significant difference in favour of PA: 3 month: 2 points* 1 year: 2.4 points* Non-significant difference: 3 year: 0.8* 5 year: 0.6*	Non-significant PA 2.3% LA 2.1%	NA
Jameson et al. 2014	UK Registry-based Baseline data	PA: 2,387 LA: 1,494	Primary OA	PA with repair? LA, Hardinge	6 months (PRO) 1 year (complications)	OHS	Significant difference of in favour of PA: 1.5-1.9 points*	Revision rate (surrogate measure for dislocations) 0.1-0.2% for both PA and LA	NA
Lindgren et al. 2014	Swedish Registry -based Baseline data	PA: 24,358 LA: 17,875	Primary OA	PA with repair? LA, Hardinge/Gammer	1 and 6 year	EQ-5D EQ-5D-index EQ-VAS	Significant difference in favour of PA: EQ-5D-index at 1 year: -0.03 [-0.03 to 0.02] EQ-VAS at 1 year: -1.5 [-1.0 to -2.0]	NA	NA
Amlie et al. 2014	Norwegian Registry -based No baseline data	PA: 421 LA: 431	Primary OA	PA with repair? LA, Hardinge	1-3 year	HOOS Pain Symptoms ADL Sport/rec. QOI	Significant difference in favour of PA -3.6 [-6.3 to -0.9] -3.2 [-6.1 to -0.4] -4.0 [-6.8 to -1.3] -4.6 [-8.6 to -0.6] -3.7 [-7.2 to -0.3]	Non-significant Self-reported PA 2.4% LA 3.7%	Self-reported PA 12.8% LA 24.8% Significant difference in favour of PA
Smith et al. 2012	UK Registry -based No baseline data	PA 665 LA 245	Not specified All consecutive THA from one centre between 2004-2006	PA with repair? LA ? No description of any of the approaches	1-3 years	WOMAC Subscales Odds ratio	Higher odds ratios for a better outcome in the PA group: Physical function: 1.3 [1.0 to 1.7] Pain: 1.6 [1.3 to 2.1] Satisfaction: 2.0 [1.5 to 2.6]	PA: 1.1% LA: 1.7%	NA

RCT= randomised controlled trial; NA=not analysed; PA with repair? = no information about whether repair of the capsule and external rotators was performed; ?= no detailed information about approach; * confidence interval not available.

Limping

Patients in the PA group reported less limping at 12 months follow-up compared with the LA group, which may be explained by the disturbance of the hip abductor muscles in the LA group [28, 40, 81]. Results from Study 3 confirmed a deficit in hip abductor and flexor muscle strength, but not in overall gait function in the LA group. The between-group difference in limping score was 0.4 point on the 4-point Likert scale and became non-significant in the per-protocol analysis. Therefore, some caution must be emphasised when interpreting the results about limping.

Our results are in line with a large cohort study that reported twice as many patients in the LA group with self-reported limping 1-3 years post-operatively [28]. That study also showed a marked difference in the five HOOS subscales between patients with and without self-reported limping in favour of the non-limping patients [28]. The patients without limping had a mean score of 17 to 35 points higher on all subscales. Post-hoc analyses of our data revealed similar differences when the patients, irrespective of surgical approach, were categorised into two groups: one with self-reported limping and one without self-reported limping, Table 15. Patients in the group without limping had significantly better outcomes on the HOOS-subcales, Table 15.

Based on our results and the existing literature, self-reported limping seems to be more pronounced in the LA group compared with PA and limping also seems to influence the PROs negatively. However, this needs to be further investigated in prospective intervention studies aiming at reducing limping gait. Furthermore, these results lead to the hypothesis that some patients in the LA group suffer from more limping and thus report more severely reduced PROs influencing the overall mean of PROs in the LA group.

Comparison of revision rates between PA and LA

Table 18 lists four registry studies that have compared the revision risk due to dislocation between PA and LA. One of the studies also included analysis of the overall risk of revision due to any cause, including aseptic loosening, infection and dislocation.

The studies found a relative risk (RR) of revision due to dislocation in the PA group varying between 1.3 and 3.3 compared with LA [34, 45, 148, 158]. However, three of the studies included patients with femoral neck fractures and/or sequela after femoral neck fractures [34, 45, 158]. Patients with femoral neck fractures have a higher risk of dislocation and revision due to dislocation than patients with primary OA as indication for THA [148, 159]. Thus, the results may not be directly applicable to the population of patients with primary OA.

Dislocation is a leading cause of revisions following THA [11]. It has been estimated that 20 to 66% of patients who experience a dislocation eventually require revision surgery [160, 161]. Kwon et al. 2006 showed in a meta-analysis that PA without soft tissue repair had a relative risk of dislocation of 8.2 [95% CI: 4.05–16.67] compared with PA with soft tissue repair [162]. It is likely that more attention to this issue within recent years has changed the procedure of PA to be performed with soft tissue repair, as done in this trial. In addition, the change toward the use of larger heads has reduced the risk of revisions due to dislocation [34, 148, 163]. Therefore, the relative risk of revision due to dislocation found in the studies listed in Table 18 may no longer be representative of the outcome today.

An increased risk of revision due to aseptic loosening in the LA group was shown by Lindgren et al. 2012 [158]. In contrast, Arthursson et al. 2007 also evaluated the risk of revision due to aseptic loosening, infection and any reasons for revision and found no difference in risk of revision between the two approaches [45].

The choice of stem and cup also influence the revision rate as shown by Byström et al. 2003 [34]. But Byström et al. 2003 did not investigate if the surgical approach had any influence on the revision risk in subgroups based on prosthetic concepts.

On the contrary, both the study by Arthursson et al. 2007 and Lindgren et al. 2012 performed subgroup analyses on patients treated with the Exeter stem. In this Exeter stem subgroup, they found no difference in revision rates between the PA and LA groups for any reason,

including aseptic loosening. This indicates that the prosthetic concept also plays an important role in revision rates [45, 158].

Based on the literature outlined in Table 18, there seems to be an increased risk of revision due to dislocation for patients in the PA group, and one study showed an increased risk of revision due to aseptic loosening in the LA group, but no difference in the overall revision rates were reported when any cause of revision was analysed [45].

Table 18. Studies comparing revision rates in patients with PA versus LA

Study	Design	Number of hips	Diagnosis and prosthetic concepts	Approach	Follow-up	Revision rate due to dislocation [95% CI]	Revision rate due to any cause, aseptic loosening or infection [95% CI]	Influence of stem and cup type	Level of evidence
Byström et al. 2003	Norwegian registry-based	PA: 9,940 LA: 32,682	All-incl. sequel after fractures Mixed cemented and cementless	PA with repair? LA Hardinge or Gammer	1987-2000	FRR = 1.9 [1.4–2.5] in favour of LA	NA	NA	II
Arthursson et al. 2007	Norwegian registry-based	25,306 Number of LA and PA not clearly described	More than primary OA-excl. fractures Only cemented	PA with repair? LA Hardinge or Gammer	1987-2004	RR = 1.9 [1.1–3.2] in favour of LA	Any cause: No significant difference Aseptic loosening: No significant difference Infection: No significant difference	No difference in revision rates between PA and LA in the subgroup of patients treated with Exeter Polished stem regarding dislocation, aseptic loosening and infection	II
Lindgren et al. 2012	Swedish registry-based	PA: 66,704 LA: 23,958	All-incl. all fresh and seq. after fractures Only cemented	PA with repair? LA Hardinge or Gammer	1992-2009	Lubinus SPII RR = 1.4 [0.15–0.6] Spectron EF Primary RR = 3.3 [2.5–10.0] in favour of LA	Aseptic loosening : Lubinus SPII RR = 1.3 [1.0–1.6] Spectron EF Primary RR = 1.6 [1.0–2.5] Both in favour of PA Infection: No significant difference	No difference in revision rates between PA and LA in the subgroup of patients treated with Exeter Polished stem regarding dislocation, aseptic loosening and infection	II
Hailer et al. 2012	Swedish registry-based	PA: 41,904 LA: 35,459	All-incl. fractures Mixed cemented and cementless	PA with repair? LA Hardinge or Gammer	2005-2010	RR = 1.3 [1.1-1.7] in favour of LA	NA	NA	II

RCT= randomised controlled trial; NA=not analysed; PA with repair? = no information about whether repair of the capsule and external rotators was performed; RR=relative risk; FRR=Failure Rate Ratio

Associations between GDI and other clinical outcomes

True validation of the GDI in the hip OA patient group is difficult because, to our knowledge, no gold standard for measuring gait 'quality' exists. However, it is relevant to investigate associations between the GDI and other clinical outcomes, as this has also been done for other patient groups [70, 71, 73]. This will gain knowledge about this composite gait index of gait 'quality' in the patients with hip OA.

In Study 1, we found weak to moderate association between the GDI and hip flexion and abductor iMVC. Further a moderate association between the GDI and pain measured in direct relation to walking was observed, but no association with pain measured over the last week was found.

These findings are in line with previous studies that reported weak to moderate associations between hip abductor muscle strength and discrete kinematic variables during gait in hip OA patients and healthy older adults [63, 164].

The importance of hip abductor muscle strength during gait has also been emphasised by others, although they did not directly measure the associations between abductor muscle strength and gait function. These studies have shown deficits in both hip abductor moment and trunk inclination that may be caused by hip abductor weakness [57-59]. Collectively, our results and earlier findings indicate that hip muscle strength, and especially hip abductor muscle strength, is important for gait function, measured with both discrete variables and with the GDI as a composite gait index.

No study has to our knowledge investigated if pain experienced in direct relation to gait has any influence on gait function in patients with primary OA. We measured pain in direct relation to walking using the NRS score. Our finding suggests that the pain level experienced directly in relation to gait is moderately negatively associated with gait 'quality'. This is in contrast to our results where we investigated associations between the GDI and pain measured over the last week using HOOS-Pain, where we found no significant associations.

The lack of an association between GDI and HOOS-Pain is supported by Behery and Foucher 2014 and Zeni et al. 2014 who investigated the association between pain, measured as the

averaged over the last week, and discrete 3-DGA parameters and found no association in patients with hip OA [63, 165].

The divergence in our results could be explained by the way the two pain scores are collected. The NRS score is directly related to the pain level experienced by the patient at the time of walking, whereas the items in HOOS-pain subscale cover several situations over the last week, not only related to the activity of walking. This exemplifies the different nature of the outcomes measuring different aspects of the construct of pain.

In summary, the results from Study 1 suggested that improvements in hip muscle strength (especially hip abduction), decreased pain levels and increased PROs, to a moderate degree, would be reflected in improved gait 'quality' measured with the GDI. However, causality cannot be established in this cross-sectional study and this needs to be investigated in a prospective intervention study.

Gait function and surgical approach

Based on the significant associations between GDI and hip muscle strength, pain and PROs found in Study 1 and given the intervention with THA surgery aiming at removing hip pain, improving PROs and hip muscle strength, we expected to find improvements in the GDI post-operatively, but surprisingly that was not the case.

The results from Studies 2 and 3 showed improved PROs, reduced pain and improved hip muscle strength in both treatment groups. Also many of the other aspects of gait function measured, namely the temporo-spatiale parameters and kinematic ROM variables from the hip sagittal and frontal planes improved post-operatively in both groups. The GDI was constant at ≈ 88 points in both groups, therefore no difference in GDI was observed at any time during follow-up between the two treatment groups, Figure 10.

This may be explained by several factors.

The results in Study 1 were based on hip OA patients investigated in a cross-sectional design and the results may not be applicable in an intervention study with THA surgery.

The GDI as a measure of gait 'quality' may not be responsive to show any improvements in gait function in the current patient group. This is exemplified by the fact that improvements in

other aspects of gait function measured with temporo-spatial parameters and hip ROM variables were found in both groups, Table 13. The lack of responsiveness might be because the kinematics in the current patient group with unilateral hip OA are mainly affected by the disease in one hip joint compared with e.g. cerebral palsy patients where gait deficits are pronounced in many joints of the lower limbs.

The GDI includes kinematic variables from the pelvis and hip in all three planes as well as kinematics from the knee, ankle and foot. Including kinematics from the other joints might underestimate the effect of a potential improvement after THA on gait function directly related to hip joint function. This effect was also discussed as a general limitation in the use of a composite gait index in a literature review of different gait indices [126].

Also, the kinematics of the trunk, which are not included in the GDI, have been suggested as important for gait function in THA patients – especially those operated on with LA [43, 59, 166]. A recent study by Meyer et al. 2015 identified 10 discriminative discrete gait variables (5 kinematic variables and 5 kinetic variables) in hip OA patients compared with healthy controls using a principal component analysis method [167]. Thus, potentially important discriminative gait variables are not accounted for in the GDI.

Madsen et al. 2004 found that most of the patients in the LA group deviated from normal gait. Especially they found that patient in the LA group had increased trunk inclination, reduced sagittal plane range of motion, and greater loading asymmetry. Whereas, many of the PA patients presented with a gait patterns that were more normal. They concluded that patients in the PA group had a better outcome regarding gait pattern [59]. However, most of the discriminative variables included in their study were measured in mid-stance of the gait cycle and thus do not represent the overall gait pattern throughout the gait cycle. The study by Queen et al. 2013 supports our result as they did not find any difference between patients in the PA and LA group in several discrete gait variables (including both temporo-spatial, kinematic and kinetic variables) [74].

A previous study by Jensen et al. 2014 reported an improvement in the GDI of 5 points with a post-operative result of ≈ 88 points in a similar patient group to that of this trial [65]. Hence, both studies demonstrate that the gait 'quality' in THA patients does not improve to the level of able-bodied individuals. This is also in agreement with earlier studies showing that even

after a successful THA, full recovery of gait function, measured using discrete gait variables, is not achievable [58, 168].

Hip muscle strength and surgical approach

This is the first randomised controlled trial to show sustained impairments in both the hip abductor and flexor muscle strength in LA compared with PA patients one year post-operatively.

The results are consistent with our hypothesis that the surgically induced trauma to the gluteus medius and minimus causes post-operative hip abductor muscle weakness.

The most recent cohort study by Winther et al. 2015 investigating difference in hip muscle strength showed abductor muscle weakness in the affected limb 6 weeks post-operatively in patients operated on with LA compared with PA, but no difference was observed after 3 months [46], this is in line with our results at 3 months. Downing et al. 2001 found in a non-randomised cohort study no difference in isometric hip muscle strength between LA and PA patients at 3 and 12 months after surgery [86]. However, this study may be influenced by a large drop-out rate on 27% and the non-randomised design.

The difference between treatment groups in hip abductor iMVC was noticeable with a medium Cohen's *d* effect size of 0.6 (0.7 for the per-protocol analysis). These findings suggest that the difference may be clinically important.

A previous study showed that lower limb muscle strength was associated with physical function [79], and hip abductor muscle strength has also been shown to contribute positively in performance-based measures of physical function in people with unilateral total knee arthroplasty [169]. Therefore, we could have expected that both the gait 'quality' and patient-reported physical function would have been reduced in the LA group compared with the PA group. However, only the self-reported limping score was reduced in the LA group at 12 months.

Another study compared THA patients (all of whom received PA) with healthy adults and showed that the patients had 17-23% less knee muscle strength 12 months post-operatively; however, the functional test (including stair climbing, five times sit-to-stand, and the 6-minute walk) showed no significant differences between the patients and healthy adults 12 months

post-operatively [170]. Thus, despite relatively large deficits in lower limb maximal muscle strength, it seems possible to perform simple functional tests at the same level as healthy individuals. This may also apply to the patients in the LA group. However, based on our results, we cannot definitely conclude whether the deficit found in maximal hip muscle strength for the LA patients, may or may not have clinical relevance in reducing physical function, although we did not find any difference in the patient-reported physical function or UCLA activity score. Further investigation of the effect on function (e.g. walk-test, stair climbing, repeated chair rise etc.) following PA and LA is therefore needed.

Our results showed that patients in the LA group had both reduced hip muscle strength in abduction and more limping gait after 12 months compared with PA patients. This may be one step in confirming the hypothesis, that LA patients experience reduced muscle strength and therefore also more limping gait, due to the surgically induced trauma to the gluteus medius and minimus muscles, as advocated by Baker and Bitounis 1989 [82].

Pain was present pre-operatively and may have reduced the pre-operative measurements of hip iMVC in both groups [131]. However, pain probably did not cause the observed differences between the two treatment groups, since pain in relation to iMVC testing was absent in both groups post-operatively, as described in the summary of results in Study 3 page 51.

We measured the change in femoral off-set post-operatively, since a reduction in femoral off-set may contribute to abductor muscle weakness [87, 115]. We found that the femoral off-set in the PA-group was significantly increased (mean Δ femoral off-set 5.1 mm) whereas the LA group was unchanged post-operatively (mean Δ femoral off-set 0.8 mm), Table 16. This small improvement in femoral off-set and thus increase of the abductor moment arm in the PA group may contribute to the improvement in abductor muscle strength seen 12 months post-operatively, however it probably only explains some of the deficit in the LA group.

Clinical implications

Based on the results from this thesis we found no clinically relevant difference between PA and LA in most patient-reported outcomes. Some of the secondary and explorative results showed superior efficacy for patients in the PA group, namely, in self-reported limping and in hip abductor and flexor muscle strength, although these deficiencies in the LA group seem not to influence the overall gait function.

Based on the literature investigating difference in PROs, PA is found to have small but not clinically relevant better outcome. There is no overall increased risk of revision in the PA group compared with LA, although the revision rate due to dislocation is higher in the PA group.

Future research

Since only few registry-based studies have investigated the difference in risk of revision, a future large-scale non-inferior randomised controlled trial is necessary to establish if PA is not inferior to LA on important clinical outcomes, including overall revision rates.

However, such a study requires inclusion of several thousand patients with long-term follow-up > 10 years and would only be feasible in a large multicentre design.

Further investigations of how to reduce limping gait are needed. This could be performed in an intervention study evaluating the effect of focused hip muscle strength training.

Research into possible predictors (e.g. pre-operative limping gait, hip abductor muscle weakness, co-morbidities) of post-operative limping gait would be beneficial and might enable a more optimal allocation of the patient to the best surgical approach for him/her.

Finally we find it relevant to further investigate if the reduced maximal hip muscle strength found in the LA group post-operatively has any implications for the patient's actual functional capacity.

Conclusion

Based on Study 1 we concluded that:

Better hip abductor and hip flexor muscles strength were significantly moderately and weakly associated with a better gait 'quality' in patients with hip OA. Furthermore, patients with higher patient-reported physical function, quality of life and lower pain levels demonstrated better gait 'quality'. Interventions aimed at improving hip muscle strength, especially hip abduction and appropriate pain management may improve the gait 'quality' in patients with severe hip OA. This however needs to be confirmed in controlled intervention studies.

Based on Study 2 we concluded that:

We found no superior efficacy of using the PA compared with LA evaluated on patient-reported physical function, pain, physical activity or quality of life, but patients operated through the PA improved more in self-reported limping.

Based on Study 3 we concluded that:

The trial did not completely confirm our hypotheses. Following total hip arthroplasty, contrary to our first hypothesis, gait function in the group receiving the posterior approach did not improve more than the group receiving the lateral approach. However, in agreement with our second hypothesis, patients receiving the posterior approach improved more in hip abductor and flexor muscle strength at 12 months. Further investigation of the effect of reduced maximal hip muscle strength on functional capacity is needed.

Summary

English

Hip osteoarthritis (OA) is a major cause of disability worldwide. Total hip arthroplasty (THA) is a successful symptomatic treatment of hip OA and has been declared as ‘the operation of the century’. Despite its great success on important key-endpoints, not all patients are satisfied. Results based on patient-reported outcomes (PROs) have shown that some patients after THA experience a reduction in physical function, limping gait and a reduced quality of life compared to the healthy population. The choice of surgical approach is one factor that may affect the PROs, gait pattern and hip muscle strength. Worldwide, the use of the posterior approach (PA) and the lateral approach (LA) are dominating. One major difference between the two approaches is the surgical detachment of the hip abductor muscles (gluteus medius and minimus) which is only performed during the LA procedure. This surgically induced damage of the hip abductors may cause reduced hip muscle strength, changes in gait function and reduced PROs, especially those associated with physical function. The literature reveals that the optimal choice of surgical approach based on evidence from high level studies remains unclear.

Thus, the overall aim of this thesis was to investigate in a randomised controlled trial if patients with primary hip OA operated on with the PA improved more in PROs, hip muscle strength and gait function than patients operated on with LA 12 months post-operatively. The secondary aim was to explore the use of a composite gait index – the Gait Deviation Index (GDI) in the quantification of hip OA patients’ gait pathology. The GDI is thought to be a general measure of the overall gait ‘quality’. A high GDI score was hypothesised to be associated with better hip muscle strength and PROs.

Method: In total, 80 patients aged 45 to 70 years with unilateral primary hip OA were scheduled for primary cementless THA and randomised to surgery with either PA or modified direct LA. The patient-reported questionnaire Hip Disability and Osteoarthritis Outcome Score (HOOS)-Physical Function subscale was used as the primary outcome. Secondary outcomes were the HOOS-Pain, HOOS-Quality of Life, the EQ-5D-3L, UCLA activity score and a limping score. The patients completed the questionnaires pre-operatively and at 3, 6 and 12 months post-operatively. The data were analysed with the multilevel mixed linear model

analysis (with repeated measures) evaluating the mean difference in improvement between the PA and LA groups with the primary end-point being 12 months.

A subgroup of 47 patients was randomly allocated to 3-dimensional gait analysis and assessment of isometric maximal voluntary hip muscle strength (iMVC) in abduction, flexion and extension and finally pain during these tests was measured using the 'Numeric Rating Scale for Pain' (NRS). Associations between the GDI, hip muscle strength, NRS-pain and HOOS-subscale scores were analysed. The same 47 patients were also evaluated at 3 and 12 months post-operatively with the same protocol as that used pre-operatively.

Results: Seventy-seven patients were available for intention-to-treat analyses. The results showed no difference in improvement in HOOS-Physical Function between the treatment groups at 12-months: -3.3 [95% CI: -8.7 to 2.1]. All secondary outcomes showed similar results except for limping score, where PA patients improved more than LA patients: 0.4 [95% CI: 0.05 to 0.66] points on a 4-point Likert scale.

The results from the subgroup of 47 patients showed that the GDI was positively associated with hip abduction strength, hip flexion strength, HOOS-Physical Function, HOOS-QOL, and negatively associated with pain after walking. All the associations were weak to moderate and explained 13% to 25% of the variation in the GDI.

The results from the follow-up study showed no difference in between-group improvement nor within-group improvement in the GDI. However, we found a statistically significant difference in improvement in both hip abductor and flexor muscle strength in favour of the PA group: -0.20 (Nm/kg) [95% CI: -0.4 to 0.0] and -0.20 (Nm/kg) [95% CI: -0.4 to 0.0] respectively.

Conclusion: Better gait 'quality' measured with the GDI was associated with better hip muscle strength, pain and PROs pre-operatively. Patient-reported physical function, pain and quality of life in patients treated with PA did not improve more than patients treated with LA at 12 months post-operatively. However, patients in the PA group improved more in self-reported limping than the LA patients. This positive effect on limping gait in the PA group might be explained by a greater improvement in hip abductor and flexor muscle strength in the PA group. However, we found no difference in gait function between groups.

Dansk resumé

Hofteartrose er en meget udbredt sygdom og leder til smerter, nedsat fysisk funktion og nedsat livskvalitet. Når symptomerne bliver for svære kan man tilbyde en operation med en kunstig hofte (THA). Dette er en meget anderkendt behandling af svær hofteartrose og har vist rigtig gode resultater i form af lang holdbarhed af proteserne og acceptable re-operations rater. Det har dog vist sig, at nogle patienter fortsat oplever smerter, nedsat fysisk funktion med bl.a. nedsat gangfunktion og nedsat hoftemuskelstyrke samt nedsat livskvalitet. Der findes flere kirurgiske adgange til hofte, når den skal opereres og tidligere studier har givet anledning til at mistænke den kirurgiske adgang for at have betydning for patient-rapporterede resultater, den fysiske funktion, gang funktion og hoftemuskelstyrke efter operationen. På verdensplan er de to mest udbredte kirurgiske adgange den bagre adgang og side-adgang. Under operation ved side-adgang bliver den forreste del af abduktor-muskelgruppen, skåret over. Ved den bagre adgang lades denne muskelgruppe urørt, men til gengæld bliver den store baldemuskel delt og den bagerste del af hofteledkapslen åbnet. Side-adgangens kirurgiske påvirkning af bløddelene omkring hoften mistænkes at give anledning til nedsat fysiske funktion, haltende gang og nedsat abduktor-muskelstyrke. Der findes dog ingen studier, der ved hjælp af et randomiseret design og anvendelse patient-rapporterede effektmål har klarlagt om den ene adgang er bedre end den anden.

Formålet med dette ph.d.-studie var at afklare om den bagre adgang var bedre end side-adgang målt på patient-rapporteret fysisk funktion, smerte og livskvalitet samt objektivt på gangfunktion og hoftemuskelstyrke efter 12 måneder. Desuden ønskede vi at undersøge om Gait Deviation Index (GDI), som er et gang-'kvalitets' index, var associeret med hoftemuskelstyrke og de patient rapporterede resultater.

Metode: Vi inkluderede 80 patienter diagnosticeret med primær ensidig hofteartrose uden tidligere operationer i benene og uden svær co-morbiditet. Ved et tilfældighedsprincip blev de allokert til operation med henholdsvis side-adgang eller bagre adgang. Inden operation blev 47 patienter tilfældigt udvalgt til at deltage med måling af deres gangfunktion og hoftemuskel styrke i ganglaboratoriet. Patienterne gangfunktion blev evalueret præ-operativt og 3 og 12 måneder efter operation. Patienterne svarede på spørgeskemaer præ-operativt, 3, 6 og 12 måneder efter operation.

Resultater: Der kunne foretages analyser på 77 patienter. Vi fandt en ikke-signifikant forskel i patient-rapporteret fysisk funktion på -3.3 [95% CI: -8.7 to 2.1] point. Vi fandt lignede ikke-signifikante forskelle på de øvrige patient-rapporterede effektmål undtagen for spørgsmålet om haltende gang. Her fandt vi at patienterne opereret med bagre adgang forbedrede sig mere over 12 måneder end patienterne opereret ved side-adgang.

I det præ-operative studie baseret på 47 patienter, fandt vi moderate associationer mellem GDI og hoftaabduktor-muskelstyrke, patient-rapporterede effektmål og smerte. De enkelte variable kunne forklare mellem 13 og 25% af variationen i GDI.

Vi fandt ingen forbedring af GDI over tid for nogen af grupperne og derfor heller ingen forskel mellem grupperne. Men for henholdsvis abduktor og fleksor-muskelstyrken forbedrede patienterne i bagre adgang gruppen sig signifikant mere end patienterne opereret ved side-adgang: -0.20 (Nm/kg) [95% CI: -0.4 to 0.0] og -0.20 (Nm/kg) [95% CI: -0.4 to 0.0].

Konklusion: Gang-'kvalitetes'-indexet 'GDI' var moderat associeret med hoftaabduktor-muskelstyrken, smerte, fysisk funktion og livskvalitet.

Der var ikke forskel mellem grupperne på patient-rapporteret fysisk funktion, fysisk aktivitet, smerte og livskvalitet efter 12 måneder. Dog fandt vi, at patienter opereret med side-adgang rapporterede mere haltende gang end patienterne opereret med bagre adgang efter 12 måneder og vi fandt reduceret hoftaabduktions- og hoftefleksions-muskelstyrke i gruppen af patienter opereret med side-adgang. Vi fandt ingen forskel på gangfunktion mellem de to grupper.

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