Statistical Analysis Plan (SAP)

Targeted exercise and changes in patient-reported symptoms and pelvic tilt in patients with acetabular retroversion - a feasibility and prospective cohort study

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INTRODUCTION

Acetabular retroversion is a specific variant of hip dysplasia, (1, 2), where the hemipelvis is externally rotated around a sagittal axis, rather than a local osseous protuberance of the superior acetabulum (3). As a result of retroversion, anterolateral cover for the femoral head is more extensive than normal, enhancing the risk of pincer-type femoroacetabular impingement syndrome (FAIS), caused by abnormal early contact between the femoral neck and anterior acetabular rim (1). FAIS is associated with pain (4), reduced level of function (5), decreased health-related quality of life (6), and early development of osteoarthritis (OA) of the hip (7, 8).

The appearance of a retroverted acetabulum is primarily verified on the anterior-posterior (AP) radiograph by the cross-over sign (COS; anterior acetabular rim crosses the posterior rim) and the posterior-wall sign (PWS; posterior acetabular rim is medial to the center of the femoral head) (1). The prevalence of radiographic signs of acetabular retroversion, on the combined presence of COS and PWS, is 5-7% among the general population (8-10). Currently, the standard treatment for symptomatic acetabular retroversion is an anteverting periacetabular osteotomy (PAO) to prevent FAIS (11). PAO is associated with risks of complications and a subsequently long period of rehabilitation.

The hip joints are directly affected by the position of the pelvis. The pelvis is balanced on the femoral heads via the acetabular sockets, carrying the load of the upper body (12, 13). Anterior pelvic tilt is an anteversion of the pelvis around a bicoxo-femoral axis in the sagittal plane and is positively correlated with lumbar lordosis in standing (13-17). A higher degree of anterior pelvic tilt functionally increases superior femoral head cover (1, 18), and thereby increases the risk of FAIS (19). Especially in standing, sitting, and squatting positions, the level of anterior tilt has been found to correlate with FAIS (20). Thus, excessive anterior pelvic tilt may cause or enhance FAIS in patients with acetabular retroversion. A systematic review and meta-analysis (21), on various causes of FAIS, concluded that physical therapy has positive short-term results on self-reported pain and function. Recent studies on exercise interventions for various types of FAIS patients included exercises aiming at improving general core stability, pelvic control, and advice on posture (22-28). However, there is currently no evidence on non-surgical treatment of reducing excessive anterior pelvic tilt, including patients with acetabular retroversion (29).

To our knowledge, this is the first study investigating a targeted exercise intervention aiming at reducing symptoms and anterior pelvic tilt in patients with acetabular retroversion. Feasibility will be assessed as it may be of importance to the outcome of a progressive home-based exercise intervention in patients with symptomatic acetabular retroversion.

Objective

To investigate feasibility of an 8-week progressive home-based exercise intervention and change in patient-reported symptoms and pelvic tilt, in a prospective cohort of patients with radiographic verified acetabular retroversion, and excessive anterior pelvic tilt.

Primary hypothesis:
In a paired design, the improvement in ´*The Copenhagen Hip and Groin Outcome Score*´ pain-subscale (HAGOS questionnaire), following an 8-week exercise intervention, will be larger in comparison with the prior control period.

Secondary hypotheses:

- The exercise intervention is feasible in terms of adherence to exercise, exercise-related pain, drop-outs, and adverse events.
- The improvements in the remaining HAGOS subscale scores on symptoms, level of function, and quality of life, following an 8-week exercise intervention, will be larger in comparison with the control period.
- The improvements in the EQ-5D-3L questionnaire, following an 8-week exercise intervention, will be larger in comparison with the control period.
- The reduction in the degree of anterior pelvic tilt evaluated by EOS imaging, following an 8-week exercise intervention, will be larger in comparison with a control period.

STUDY METHODS

Design

The study was designed as a single-center, non-consecutive, unblinded prospective cohort study using patients as their own controls. The change between an 8-week control period prior to the intervention and the following 8-week exercise period will be reported.

Exercise intervention

A physiotherapist (the project manager) informed the patients about the relation between the hip condition and the purpose of the exercise program, provided advice on activity and sports modification, and instructed in exercises. The exercise program was an 8-week progressive home-based exercise intervention with optional, supervised booster-sessions and opportunity to contact the project manager by mail or phone in case of questions regarding the exercise program. After the 8-week exercise period was completed, the patients were encouraged to continue with the exercise program for another 16 weeks.

The exercise program was standardized and non-supervised consisting of four general elements: stretching for posterior pelvic tilt mobility, strengthening hip abductors and extensors, improving body core stability, and movement control for actively tilting and/or keeping the pelvis posteriorly.

Each exercise session began with stretching exercises, followed by muscle strength training and ended with specific posture improving exercises on tilting the pelvis posteriorly.

The exercise program was intended to be completed three to four times a week, with a rest day in between. In the first two weeks (module I), the duration of the exercise program was approximately 30 minutes to complete. For the remaining six weeks (module II), the exercise program gradually took longer time to complete (i.e. 45 min.), as the number of repetitions increased.

In case of any adverse events, or other challenges related to the exercise program, the project manager was contacted, and a booster-session was arranged. In cases of drop-outs, the referring physician decided whether the patient should be seen in the outpatient clinic again.

Experienced hip-related pain exceeding 4 on a 0-10 scale, where 0 = *no pain* and 10 = *worst possible pain,* was considered as alarming pain and the exercises was subsequently adjusted. The level of pain before, during, and after exercise were noted in the training diary along with the use of over-the-counter analgesics.

Overview of the progression of exercises

Module I – Exercises (first two weeks)	**Week 1-2**
#1 Stretching the anterior hip	2 sets of 30 sec.
#2 Stretching the low back	2 sets of 30 sec.
#3 Stretching the anterior thigh	2 sets of 30 sec.
#4 Strengthening the hip abductors	2 sets of 10 reps.
#5 Strengthening the hip external rotators (Clamshell)	2 sets of 10 reps.
#6 Spinal mobility (Cat & Camel)	1 set of 10 reps.
#7 Core stability (Bird Dog)	3 sets of 10 reps.
#8 Movement control in lying (Pelvic tilt)	2 sets of 10 reps.
#9 Core stability (Static plank)	2 sets of 15 sec.
#10 Strengthening the abdominal muscles (Crunch)	2 sets of 10 reps.
#11 Strengthening the abdominal muscles (Oblique crunch)	2 sets of 10 reps.
#12 Movement control in standing (Supported pelvic tilt)	1 set of 10 reps.
#13 Movement control in standing (Unsupported pelvic tilt)	1 set of 10 reps.

Module II – Exercises (from week 3 to 8)	**Week 3-4**	**Week 5-6**	**Week 7-8**
#1 Stretching the anterior hip	2 sets of 30 sec.	2 sets of 30 sec.	2 sets of 30 sec.
#2 Stretching the low back	2 sets of 30 sec.	2 sets of 30 sec.	2 sets of 30 sec.
#3 Stretching the anterior thigh	2 sets of 30 sec.	2 sets of 30 sec.	2 sets of 30 sec.
#4 Strengthening the hip abductors	2 sets of 10 reps.	3 sets of 10 reps.	4 sets of 10 reps.
#5 Strengthening the hip external rotators (Clamshell)	2 sets of 10 reps.	3 sets of 10 reps.	4 sets of 10 reps.
#6 Spinal mobility (Cat & Camel)	1 set of 10 reps.	1 set of 10 reps.	1 set of 10 reps.
#7 Movement control in lying (Dying bug)	2 sets of 10 reps.	3 sets of 10 reps.	4 sets of 10 reps.
#8 Movement control in lying (Single leg pelvic tilt)	2 sets of 10 reps.	3 sets of 10 reps.	4 sets of 10 reps.
#9 Strengthening the hip extensors	2 sets of 10 reps.	3 sets of 10 reps.	4 sets of 10 reps.
#10 Core stability (Dynamic plank)	2 sets of 10 reps.	3 sets of 10 reps.	4 sets of 10 reps.
#11 Movement control in standing (Sup. pelvic tilt)	1 set of 10 reps.	1 set of 10 reps.	1 set of 10 reps.
#12 Movement control in standing (Unsup. pelvic tilt)	1 set of 10 reps.	1 set of 10 reps.	1 set of 10 reps.

Abbreviations: Sec.=Seconds, Reps. Repetitions, Sup.=Supported, Unsup.=Unsupported

Selection of subsample for physical performance assessment

A subsample (20 patients) of the included patients was randomly selected to be investigated for isometric muscle strength, kinematic and kinetic outcomes during gait and functional tasks in a 3-dimensional motion laboratory. The explorative outcomes will be reported in secondary analyses not specified in the current SAP.

Sample size

The sample size calculation was based upon paired means calculation. The minimal clinical important difference (MCID) for the HAGOS pain-subscale was estimated being 10 % (half a standard deviation) (30). A minimum of 36 patients was required (10 % pre-posttest difference on HAGOS pain-subscale, SD=20.6 (30), alpha = 0.05, power = 80 %). An additional of four patients were added due to the risk of dropout.

Stopping guidance

There was no overall stopping guidance in the study or interim analysis of adverse effects. However, the training was stopped, and the referring physician contacted if individual patients experienced pain above 4 on a 0-10 Numeric Ranking Scale related to the training program, that could not be reduced by adjusting the exercises during a booster-session.

Timing of analysis

The primary endpoint was after the 8-week exercise period.

There were four time points at which the outcomes were measured, framing three consecutive periods: control period, exercise period, and an additional 16-weeks exercise period. Analysis of data from the 16 weeks of additional exercise is not a part of this SAP.

Timing of outcome assessments

Time points at which the outcomes were measured are presented in Table 1. Outcomes are defined in the *Analysis* section.

Table 1 – Timing of outcome assessments

Outcomes	Control period	Baseline	Primary endpoint
	Minus 8-weeks before exercise intervention	Start-up of exercise intervention	End of 8-week exercise intervention
Primary outcome			
PROM:			
HAGOS *pain* subscale	x	x	x
Secondary outcomes			
PROM:			
HAGOS remaining five subscales	x	x	x
EQ-5D-3L	x	x	x
EOS scanning:			
Pelvic tilt	x	x	x
Explorative outcomes			
PROM:			
Global Perceived Effect			x
Oxford Hip Score	x	x	x

Abbreviation: PROM (Patient-Reported Outcome Measure)

STATISTICAL PRINCIPLES

Descriptive data and fitted regression residuals from the mixed-effects linear regression model will be visually assessed for Gaussian distribution by use of QQ-plots and frequency histograms, and statistically tested using the Shapiro-Wilk test. Parametric and/or non-parametric statistical analyses will be used appropriately. A two-tailed P-value of $P \leq 0.05$ will be considered statistically significant, and estimates will be presented with 95% confidence intervals. A primary analysis following the Intention-To-Treat (ITT) principle and a secondary Per Protocol (PP) sensitivity analysis will be conducted (elaborated later in the *Analysis* section).

Adherence

Adherence to the exercise program (frequency) was recorded in a self-reported training diary. Adherence was defined as at least 75% completion of the prescribed exercise program in the 8-week period. The patients were instructed to exercise 3-4 times a week (i.e. 24-32 times over eight weeks) accordingly. Thus, at least 18 exercise sessions (75% of 24 exercise sessions), must have been completed to achieve acceptable compliance.

Exercise-related pain and adverse events

Exercise-related pain was recorded in a self-reported training diary, from 0-10 on a Numeric Ranking Scale (NRS) before, during and after exercising. A level of hip-related pain equal to and above 5 was defined as alarming values and subsequently adjustments were done as described above. Potential adverse events were noted in the training diary or reported by phone and email to the project manager. The use of hip-related analgesics and general comments on the exercise program were noted in the diary.

Protocol deviations

The following minor adjustments/additions were made after trial registration on Clinicaltrials.gov and inclusion of the first patient.

- The assessment of feasibility was added to the study objective because of the novelty and potential importance of the exercise program.
- The secondary outcome *´Radiographic measurement of pelvic tilt in the frontal plane, defined as the distance (in mm.) between the sacro-coccygeal joint and the symphysis´* was changed to the *´Radiographic measurement of pelvic tilt in the sagittal plane, defined as the angle (in degrees) between a horizontal line and a line connecting the upper border of the symphysis with the sacral promontory´*. From inspecting our radiographic data, we learned that pelvic tilt measured in the sagittal plane were more reliable compared to frontal plane images. Moreover, the adjustment resulted in that no images had to be excluded due to poor image quality.
- Due to two dropouts early in the study, two additional patients were recruited. However, since only one patient subsequently dropped out, a total of 39 patients completed the training out of 42 included patients.
- Three patients did not get the last EOS-scanning done after the end of the exercise period due to pregnancy (n=2) and a defect apparatus (n=1).

TRIAL POPULATION

Patients between 18 to 40 years old were included from Odense University Hospital outpatient clinic (Denmark), with verified acetabular retroversion (positive COS and PWS) from a frontal pelvic radiograph in standard standing position, not eligible for periacetabular osteotomy and able to take part in the intervention. Patients were excluded if they had a pelvic-tilt-ratio greater than 0.5 (31) (the height of the obturator foramen divided by the height of the lesser pelvis) indicating posterior pelvic tilt, radiographic sign of hip osteoarthritis (< 2 mm. joint space), previous lumbar, pelvic or hip related surgery, conditions not allowing exercise therapy, a body mass index (BMI) above 35 and not understanding spoken and/or written Danish language.

Flowchart of patients´ progress through the study is presented in Figure 1.

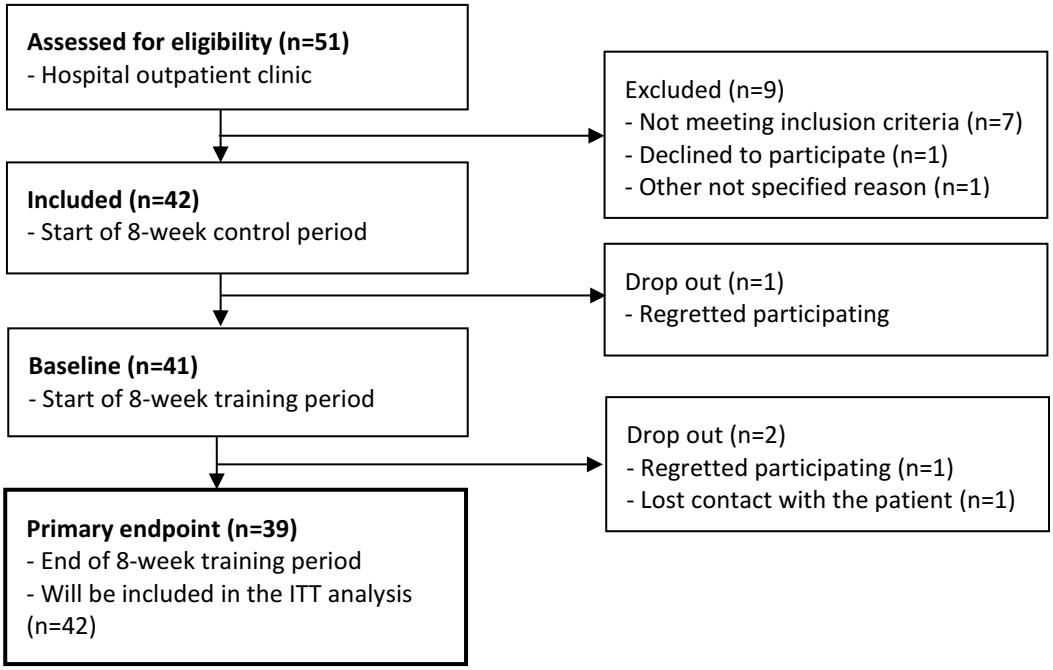

Figure 1 – Flowchart of patients´ progress through the study

Patient characteristics are presented in Table 2.

Table 2 – Patient characteristics at the beginning of the control period (n=42)

Patient characteristics
Sex, male/female, n (%)
Age, years
BMI, kg/m^2
Height, m
Weight, kg
Affected hip
Bilateral, n (%)
Left, n (%)
Right, n (%)
Patient-reported outcome measures
HAGOS, score from 0 to 100
Pain
Symptoms
Physical function in daily living
Physical function in Sport and Recreation,
Participation in Physical Activities
Hip and/or groin-related Quality of Life
EQ-5D-3L, index score
Pelvic tilt
Pelvic tilt, degrees

Abbreviations: BMI (body mass index), FAIS (femoroacetabular impingement syndrome), n (numbers)
* Gaussian distributed data will be presented as standard deviation (SD), otherwise as median and interquartile range (IQR)

ANALYSIS

Primary outcome definitions

Between-period change in condition-specific questionnaire The Copenhagen Hip and Groin Outcome Score (HAGOS) *pain* subscale on a 0-100 scale, with zero representing extreme hip and/or groin problems and 100 representing no hip and/or groin problems (30). HAGOS has shown good evidence of reliability, validity and responsiveness in young to middle-aged patients with longstanding hip and/or groin pain (55, 56).

Secondary outcome definitions

1. Between-period change in the remaining five HAGOS-subscales (30) (*Symptoms*, *Physical function in daily living*, *Physical function in Sport and Recreation*, *Participation in Physical Activities* and *hip and/or groin-related Quality of Life*).

2. Between-period change, in the generic questionnaire European Quality of Life - 5 Dimensions (EQ-5D-3-Levels) questionnaire (32), (index value set for Denmark). The upper EQ-5D index value = 1 indicates full health (indicated by "no problem" in all domains), whereas EQ-5D index value = 0 represents death. In addition, the overall health state the actual day is marked on a numeric scale on which the best state is marked 100, and the worst state is marked 0. Psychometric properties for EQ-5D-3L in patients having FAIS is not reported, but EQ-5D-3L is validated as a generic measure of general health (33).

3. Between-period change in pelvic tilt (in degrees) was measured with EOS scanning in standing position in the sagittal plane as the angle between a horizontal line and a line connecting the upper border of the symphysis with the sacral promontory (34).
   EOS® imaging system is a low-radiation roentgen scanner capturing the selected body part of a person in a standardized standing position with the option to acquire orthogonal views simultaneously in the frontal- and sagittal plane (35). EOS provides diagnostic qualities similar to conventional X-ray using 44 % less radiation when radiographic signs of acetabular retroversion are assessed (36). EOS® imaging system has shown excellent reliability in measuring the sagittal alignment of the pelvis (37). In comparison with radiographs, EOS® is found valid (38) and reliable (39) in assessing pelvic configurations.

Data quality

All patient-reported outcomes will be entered twice to check for entry errors. Fifty randomly selected sagittal EOS scans across the three time points will be assessed for inter-observer reliability regarding pelvic tilt.

Analysis methods

Repeated measurements from a particular patient are likely to be more similar to each other than measurements from different patients, and this correlation needs to be considered in the analysis of the resulting data (40). Longitudinal measurements are not independent of one another, due to the individual baseline value, and time factor, which must be taken into account (40).

A mixed-effects linear regression model will be used accordingly to the longitudinal design and will accommodate missing data in the analysis under the assumption "missing at random," thus, the analyses will follow the *Intention To Treat* (ITT) principle (40).

Primary analysis:

Under the assumption of normal distributed residuals, a mixed-effects linear regression model will be used to investigate the between-period change on the dependent continuous outcome variable (HAGOS subscale pain). A dummy-coded variable, indicating the three time points at which the measurement was taken, is framing the control period and the intervention period.

Sensitivity analysis:

A *´Per-Protocol analysis´* for patients demonstrating the a-priori-defined acceptable adherence to exercise (≥75%) will be performed.

Secondary analysis:

Change between-period comparisons in the remaining five HAGOS subscales, EQ-5D-3L, and pelvic tilt will be tested using a mixed-effects linear regression model as described in the primary analysis.

Post hoc analysis:

A responder/non-responder analyses will be carried out by investigating the exercise period change on the HAGOS pain subscale (Y-axis) against HAGOS pain subscale baseline score, pelvic tilt, age and BMI (X-axis), respectively. The *Minimal Clinical Important Difference* (MCID) of 10 % in the HAGOS pain subscale (30) will be marked as a horizontal lines (Y=±10). Patients with change scores equal to and larger than the MCID will be defined as responders to the exercise intervention.

Table 3 – Outcome change scores

	Control period change Mean, [95% CI], P-value	**Exercise period change** Mean, [95% CI], P-value	**Between periods change** Mean, [95% CI], P-value
Primary outcome			
HAGOS pain			
ITT			
PP			
Secondary outcomes			
HAGOS symptoms			
ITT			
PP			
HAGOS ADL			
ITT			
PP			
HAGOS Sp/Re			
ITT			
PP			
HAGOS Ph/Ac			
ITT			
PP			
HAGOS QoL			
ITT			
PP			
EQ-5D-3-L			
ITT			
PP			
Pelvic tilt			
ITT			
PP			

Abbreviations: ITT=Intention To Treat (Mixed-effects linear regression model), PP=Per Protocol, ADL= *Physical function in daily living,* Sp/Re= *Physical function in Sport and Recreation*, Ph/Ac= *Participation in Physical Activities*, QoL= *hip and/or groin-related Quality of Life*

Clinical perspective

This study will provide information regarding feasibility and responder characteristics of a standardized progressive home-based training intervention for patients with symptomatic acetabular retroversion and excessive pelvic tilt.

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