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Title: «Evaluation of physical function, Quality of Life and Hip- and Knee Osteoarthritis Minimum 15 years After femoral Lengthening».

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Introduction

Limb lengthening is an established method for treatment of leg length discrepancy (anisomelia) or short stature (Castelein & Docquier, 2016; Steen, Terjesen, & Bjerkreim, 1997). The most common cause of limb lengthening is anisomelia (Castelein & Docquier, 2016). Anisomelia can either be innate or acquired, for instance after an injury (Castelein & Docquier, 2016). At Oslo University Hospital, it is performed 15-20 lower extremity lengthening procedures yearly including tibial and femoral lengthening. The vast majority of these are performed on patients with congenital deformities or other skeletal pathologies, and only a few are without a clear diagnosis or with acquired leg length discrepancy. Leg length discrepancy can be problematic as it often causes pelvic tilt towards the short side (Steen et al., 1997). This again, can cause functional scoliosis, largely affecting the gait (Steen et al., 1997). It is documented that anisomelia of more than two cm should be treated (Steen et al., 1997). Treatment could be either conservative by using shoe lift or surgical, where the long leg could be shortened or the short leg lengthened (Steen et al., 1997). In growing children there´s also the possibility to stop growth in the long leg at a certain time to achieve leg length equality (isomelia) (Steen et al., 1997). In many patients, limb lengthening will of various reasons be preferred, if the discrepancy is over three cm (Steen et al., 1997).

There are described several limb lengthening methods, for instance the Wagner method and the Ilizarov technique (Ilizarov, 1988; Wagner, 1971). The callotasis principle (distraction osteogenesis or callus distraction) described by Gavril A. Ilizarov is the most trusted and accepted method (Castelein & Docquier, 2016; Paley, 1990), and all patients invited to participate in this project are lengthened with callotasis. With the callotasis method the bone is stabilized at least two places with a fixator before the surgeon makes a corticotomy between the fixations (Ilizarov, 1988). Bone and soft tissue are lengthened by regeneration under conditions of tension stress when the bone fragments on each side of the corticotomy is pulled apart, usually 0.75 - 1 mm a day distributed over three to four sequences until goal of lengthening is achieved (Ilizarov, 1988; Maffulli, Pattinson, & Fixsen, 1993; Paley, 1990).

In our study we will concentrate on femoral lengthening as it appear more homogenous than tibial regarding healing and complications (Maffulli et al., 1993). In addition, unlike tibia, femur has large two-joint muscle groups surrounding it (Maffulli et al., 1993), making it more relevant for us investigating adjacent joint function than with tibial lengthening. Most patients

regain full range of motion in their hip and knee after femoral lengthening with callotasis (Barker, Simpson, & Lamb, 2001; Bhave et al., 2017; Herzenberg, Scheufele, Paley, Bechtel, & Tepper, 1994; Holm, Steen, Ludvigsen, & Bjerkreim, 1995; Horn, Grimsrud, Dagsgard, Huhnstock, & Steen, 2015; Kawoosa, Majid, Halwai, Mir, & Mir, 2004; Maffulli, Nele, & Matarazzo, 2001; Motmans & Lammens, 2008; Zambito & Aldegheri, 1997). However, limb lengthening is associated with high risk of complications, where loss of knee extension is most commonly reported (Fitch, Thompson, Rizk, Seaber, & Garrett Jr, 1996; Paley, 1990). Infections, subluxation of the hip- or knee joint, premature healing, lack of healing, development of deformities after fixator removal, fractures after conclusion of lengthening, reduced gross motor skills and more pain than healthy controls are other known complications associated with limb lengthening (Castelein & Docquier, 2016). We have found studies both indicating muscle weakness, and unchanged muscle strength after femoral lengthening with callotasis (Bhave et al., 2017; Holm et al., 1995; Krieg, Gehmert, Neeser, Kaelin, & Speth, 2018; Oey, Engelbert, & Wieneke, 1999). These are all small studies with different design and patient basis, making them hard to compare. Some studies report good functional outcome after femoral lengthening, but the measurement of function is poorly defined and described in these studies (Eralp, Bilen, Dikmen, & Eren, 2012; Zambito & Aldegheri, 1997). We have only found two studies describing health status and quality of life after femoral lengthening with callotasis. Shahcheraghi et al. (2015) found no deterioration regarding function, quality of life and health status comparing pre- and postoperative status, while Moraal et al. (2009) found that patients had physical limitations, but normal psychosocial function and self-esteem compared to healthy normal population. Quality of life were comparable to healthy normal population, except from significantly lower gross motor function, vitality, and more pain. There is lack of research on physical function, quality of life, health status and activity level after femoral lengthening with an obvious need for further research with good statement of both patient group and method.

Textbooks describing limb lengthening claims that it increases the risk of osteoarthritis (Sneppen, Bünger, Hvid, & Søballe, 2014), but to our knowledge this statement lacks research evidence and appears more like an assumption. Animal research have shown tendencies of knee osteoarthritis after femoral lengthening (Stanitski, 1994), but we have only succeeded in finding one article that describes osteoarthritis development after femoral lengthening on humans, where 18 out of 23 patients showed knee osteoarthritis with a mean follow-up of 6 years after femoral and / or tibial lengthening (Jeong, Inan, Riddle, Gabos, & Bowen, 2006).

It is an interesting finding, but this study used another lengthening method than today's gold standard of callotasis and were performed on patients with congenital femoral deficiency. It is hard to say if the osteoarthritis seen in these patients is in context with the lengthening procedure with their method of choice or the patient's pathology. It is important to know if the procedure itself increases the risk of developing osteoarthritis. In our study we will therefore only include patients with idiopathic or acquired leg length discrepancy, minimizing as far as we can the risk of the patient´s pathology being the explanatory factor for eventual findings. Socioeconomically it´s relevant to know whether limb lengthening increases the risk of osteoarthritis, as the condition leads to pain and reduced function, and can cause considerable costs regarding sick leaves, medications, physiotherapy and possibly prosthetic operations (Bitton, 2009; Grotle, Hagen, Natvig, Dahl, & Kvien, 2008). It can take time from an initial factor until osteoarthritis can be confirmed by conventional radiology, and all the research we have been able to find describing consequences of limb lengthening, all have relatively short follow-up, mostly far below ten years. With the lack of research available in the question of context between limb lengthening and risk of osteoarthritis, there is an obvious need for more research to investigate this with long enough follow-up to be able to identify osteoarthritis within the patient group.

There is of considerable value to both patients and treating health professionals to be aware of what long term consequences to expect after limb lengthening when operative or conservative strategy of treatment is to be decided. Based on this, we want to evaluate physical function, quality of life and development of hip- and knee osteoarthritis minimum 15 years after femoral lengthening due to idiopathic or acquired leg length discrepancy.

Responsibility and sponsorship

Oslo University Hospital is responsible for the study, and Sophies Minde AS has sponsored the project by granting a research scholarship paying the salary for the researcher to be able to implement this study. All data will be collected at Oslo University Hospital. Radiologic examinations will be performed by radiographic section at Oslo University Hospital, while all other data will be collected by the researcher.

Purpose of the study and research questions

The purpose of this study is to evaluate physical function (range of motion, 30 seconds sit to stand test, stair test and hop tests), quality of life, health status, activity level and development of osteoarthritis in the hip- and knee joint minimum 15 years after femoral lengthening due to idiopathic or acquired leg length discrepancy.

Research questions:

1. Are there differences in physical function in the lower extremities in patients who have undergone femoral lengthening compared to reference values?
2. Do patients who have undergone femoral lengthening achieve recommendations for physical activity?
3. Are there differences in quality of life in patients who have undergone femoral lengthening compared to reference values?
4. Are there differences in health status in patients who have undergone femoral lengthening compared to reference values?
5. Are there differences in development of osteoarthritis in lengthened and unlengthened hip- and knee joint in patients who have undergone femoral lengthening?

Design, material and method

This study is a quantitative cross-sectional study.

Patients

Includable patients for this study will be identified from protocols from the surgical department.

Inclusion criteria: Patients with idiopathic (unknown cause) or post traumatic leg length discrepancy, that has been operated with femoral lengthening with callotasis minimum 15 years ago.

Exclusion criteria: Innate skeletal pathology leading to shortening of the lower extremity, malangulation and less developed musculature, such as congenital femoral deficiency (CFD) or fibular hemimelia (Jeong et al., 2006). Patients with acquired leg length discrepancy after

infection in hip- or knee joint, and patients that have inserted hip- or knee prosthesis will also be excluded.

Data collection

All examinations will be completed at the same day at Oslo University Hospital.

Outcome measures

Physical function

Active range of motion (AROM) of the hip- and knee joint will be measured in degrees with an analog goniometer. Even though goniometric measures have uncertainties, acceptable intra-tester reliability is shown in hip and knee measurements with analog goniometer (Holm et al., 2000; Watkins, Riddle, Lamb, & Personius, 1991).

30 seconds sit to stand test (30sSTS) measures lower extremity strength (Bennell, Dobson, & Hinman, 2011; Csuka & McCarty, 1985). Chair with height of 44-45 cm will be used. The participant is told to sit and stand as many times as possible within 30 seconds, and the total number is registered (Tveter, Dagfinrud, Moseng, & Holm, 2014).

Stair test measures submaximal cardiopulmonary endurance (Cataneo & Cataneo, 2007). The participant is asked to move as fast as possible 18 stairs (17±1 cm) up and down three consecutive times. Total time in seconds is registered. The participant is allowed to run and use the banister if needed. The participant has to step on every stair. Pulse is measured, and Borg scale 6-20 registered immediately after the test (Tveter et al., 2014).

Hop tests will be used to compare function in the lengthened and unlengthened limb. The tests are developed for patients with ACL ruptures, but the high specificity and low false positive rates found is an argument for us to use it to separate the limbs from each other and confirm if there is impaired lower limb function (Noyes, Barber, & Mangine, 1991). Single hop for distance, triple hop for distance, timed hop (seconds used to hop 6 m) and cross-over hop for distance (triple cross-over hop over 15 cm wide tape) will be performed on both legs.

Questionnaires

Knee Osteoarthritis Outcome Score (KOOS) is a self-administered questionnaire. It has shown validity and reliability measuring function and pain in patients with knee injuries and osteoarthritis (Roos & Lohmander, 2003; Roos, Roos, Lohmander, Ekdahl, & Beynnon, 1998). The participant answer questions regarding pain, function, stiffness and quality of life regarding knee pain.

EQ-5D-5L has shown validity and reliability measuring health related quality of life in patients with hip- and knee pain (Fransen & Edmonds, 1999). It is a self-administered questionnaire where the participants report the extent of problems they have in the five dimensions mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The questionnaire also contains a vertical analogue scale with the labelled endpoints 0-100 giving a valuation of the participants own health state that can be used as a quantitative measure of health outcome based on the patients' own judgement. The use of this questionnaire is approved by EuroQol.

International Physical Activity Questionnaire (IPAQ) short version has shown validity and reliability, and is a self-administered questionnaire used to obtain estimates of physical activity level (Cerin et al., 2016). Participants answer the amount of time being in vigorous activity, moderate activity, walking and sitting during the last 7 days. This will be transitioned into MET-score.

Radiology

Osteoarthritis in hip- and knee joints will be evaluated by measuring joint space width (JSW) and Kellgren & Lawrence classification (KL) (Terjesen & Gunderson, 2012). Leg length equality will be evaluated with standing axis measurements. All radiologic measurements are done by an experienced radiologist at Oslo University Hospital. Lengthened side will be compared to unlengthened side.

Analyzes

AROM in the hip and knee joint: The lengthened and unlengthened side will be compared using to-sample t-test.

30Ssts: We will analyze if there is a difference between patients that have undergone femoral lengthening and reference values with Wilcoxon signed ranks test (Tveter et al., 2014).

Stair test: We will analyze if there is a difference between patients that have undergone femoral lengthening and reference values with Wilcoxon signed ranks test.

Hop tests: The results will be analyzed comparing lengthened and unlengthened side using Wilcoxon signed ranks test.

KOOS: To analyze if there is a difference between patients that have undergone femoral lengthening and reference values, one-sample t-test will be used.

EQ-5D-5L: We will analyze if there is a difference between patients that have undergone femoral lengthening and reference values with one-sample t-test

IPAQ: To analyze if the patients meet recommendations for physical activity of 600 MET, one-sample t-test will be used (ASCM, 2013).

JSW and KL: Evaluation of osteoarthritis development in the lengthened and unlengthened side will be presented by descriptive statistics.

Research ethics assessment

Possible negative consequences of this project are that the participants will have to use their time without being economically compensated, and they will be exposed to x-rays that are not medically induced. On the other hand, the participants are offered a thorough examination of their hips and knees, both clinically and radiological, in addition to participate in research that may be beneficial for other patients going through the same procedure.

Usefulness

The aim of the study is to increase knowledge about function, quality of life and risk of developing osteoarthritis after femoral lengthening. it is of importance for both patients and clinicians to be aware of possible long-term consequences of the treatment. All patients that

are treated with femoral lengthening at Oslo University Hospital nowadays, are close monitored by physiotherapist first in hospital care, and then locally after discharge. As there is lack of available research on the field, our results can be of interest for both patients, orthopedists, physiotherapists and other health care professionals.

Approvals and registrations

- Regional ethics committee: 2018/416 REK South East B.
- Data protection officer at Oslo University Hospital: 18/08589.
- Radiographic section at Oslo University Hospital: 1829.
- ClinicalTrials.gov: NCT03966573.

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