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## KNEE OSTEOARTHRITIS DEVELOPMENT FIVE YEARS FOLLOWING ARTHROSCOPIC PARTIAL MENISCECTOMY OR EXERCISE THERAPY FOR DEGENERATIVE MENISCAL TEARS: THE ODENSE-OSLO MENISCECTOMY VERSUS EXERCISE TRIAL

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**Purpose:** Degenerative meniscal tears per se and partial meniscectomy are strong risk factors for knee osteoarthritis (OA) development. Several randomized controlled trials have found that partial meniscectomy provides no clinically relevant benefit compared to exercise therapy for degenerative meniscal tears. However, long-term follow-up studies of randomized controlled trials are lacking. Hence, the aim of this five-year follow-up of the Odense-Oslo Meniscectomy versus Exercise (OMEX) trial was to compare progression of individual radiographic features of the knee, incident radiographic knee OA and changes in patient-reported outcome measures following partial meniscectomy or exercise therapy for degenerative meniscal tears.

**Methods:** One hundred and forty middle-aged patients with an MRI-verified degenerative meniscal tear and 97% without radiographic knee OA were included. Participants were randomized to either arthroscopic partial meniscectomy or a 12-weeks exercise therapy program. Tibiofemoral joint space narrowing and marginal osteophytes in the medial and lateral compartment were assessed semi-quantitatively using the OARSI atlas. The risk for progression for each individual radiographic feature was compared between groups. Additionally, a total radiographic score was calculated, and comparison made between treatment groups. Development of incident radiographic knee OA (Kellgren & Lawrence grade $\geq$2), changes in medial tibiofemoral fixed joint space width (fJSW, quantitatively assessed) and in patient-reported outcome measures (Knee injury and Osteoarthritis Outcome Score [KOOS]) were also compared between groups. Poisson regression with robust standard errors was applied to compare groups with respect to progression of the individual radiographic features and incident radiographic knee OA. The results are presented as risk ratio with 95% confidence intervals (95% CI). All models were adjusted for the stratification variable, gender. Between-group difference in change in total radiographic score was assessed by linear regression, adjusted for gender and baseline value of the outcome. Changes in medial fJSW and in all five KOOS subscales were analyzed by analysis of covariance (ANCOVA), with gender and baseline value of the outcome as covariates. Statistical analyses were performed using a full-set analysis, as well as per protocol and as treated analysis.

**Results:** Radiographic assessment at the five-year follow-up was performed on 120 participants (86%) (62 participants in the surgery group and 58 in the exercise therapy group). For the surgery group the risk ratios (95% CI) for progression of joint space narrowing and medial and lateral osteophytes were 0.89 (0.55-1.43), 1.15 (0.79-1.67) and 0.77 (0.42-1.42), respectively, compared to the exercise therapy group. The linear regression model indicated no difference between groups in the total radiographic score (B=-0.02, 95% CI -0.51 to 0.49). Sixteen percent in both groups developed radiographic knee OA over the follow-up period (Risk ratio 1.03, 95% CI 0.46 to 2.30). The mean change (95% CI) in medial fJSW was -0.50 mm (-0.69 to -0.30) for the surgery group and -0.30 mm (-0.51 to -0.09) for exercise therapy group. The between-group difference was not statistically significant (p=0.17, 95% CI -0.48 to 0.09). No statistically significant or clinically relevant differences were found between groups for the five KOOS subscales. Per protocol and as treated analysis yielded similar results to the full-set analysis.

**Conclusions:** We found no statistically significant differences in individual risks for progression of joint space narrowing, marginal osteophytes or change in total radiographic score between surgical and exercise therapy treatments for degenerative meniscal tears. Further, there was no statistically significant or clinically relevant differences between arthroscopic partial meniscectomy and exercise therapy in patient-reported outcome measures.

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## IS PHYSICAL ACTIVITY ASSESSED WITH ACCELEROMETERS MORE SENSITIVE TO KNEE PAIN THAN CONVENTIONAL FUNCTIONAL PERFORMANCE TESTS? - DATA FROM THE OSTEOARTHRITIS INITIATIVE

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**Purpose:** Functional performance measures (FPMs) represent important instruments in epidemiological and clinical trials of knee osteoarthritis, as they provide potentially more objective information than patient reported outcomes (PROs). We have shown previously that, amongst different FPMs, the Chair Stand Test (CST) is more sensitive to different levels of knee pain than the 20m and 400m walk test. Given the current interest in the use of wearables for functional evaluations in clinical trials and clinical practice, the aim of the current work was to analyze whether physical activity parameters obtained from accelerometry better discriminate between various knee pain strata than the CST.

**Methods:** The current analysis was conducted in 552 participants from the Osteoarthritis Initiative (OAI [47% women; age 65±9 years; BMI 28±4 (mean±SD)]) who had NRS (Numerical Rating Scale, range 0-10 [low-high]) pain measures for both knees at 48 months follow-up, CST results and accelerometer measurements available (ActiGraph GT1M uniaxial accelerometers; ActiGraph, Pensacola, FL). Participants with hip pain, and hip or knee joint replacement were excluded. Please note that accelerometry was an ancillary study to the OAI, and that data only were available for a subset of OAI participants, and only starting with the 48-month follow-up. Accelerometry parameters included the raw output as daily counts as well as minutes of light, moderate and vigorous activity, and moderate/vigorous activity representing the sum of the latter. Further, bout minutes of moderate/vigorous activity were available, with a bout being defined as an 8 out of 10-minute period with an intensity equal to, or greater than a given threshold. Three thresholds were used for each parameter, based on definitions from different authors (Freedson, Swartz, Troiano; Figure 1).

Participants were divided into no (NRS 0), mild (NRS 1/2), moderate (NRS 3/4) or non-acceptable pain (NRS>4) strata, based on the knee with the greater NRS value (target knee). NRS$\leq$4 had previously been defined in the literature as a patient acceptable symptom state (PASS). Mean values and standard deviations (SDs) were calculated for all accelerometry parameters as well as the CST in each pain stratum. ANCOVA was used to compare physical activity measures and the CST between participants with mild, moderate or non-acceptable pain vs. those without pain. Cohen's D was calculated as a measure of effect size. Because age and BMI were previously identified to be significantly associated with FPM outcomes in healthy subjects, additional analyses were run with adjusting for these variables.

**Results:** Of the 552 subjects, 44% had no knee pain, 19% mild, 19% moderate, and 18% non-acceptable pain in the target knee. Using definitions by Freedson and Troiano, minutes of light activity represented 91-95% of the total recorded activity across all pain strata, and vigorous activity only 0.2-0.7%. Using the definition by Swartz, light activity represented 58-61% and vigorous activity 0.4-1.3%. Moderate/vigorous activity as defined by Freedson and Troiano best discriminated between participants with non-acceptable vs. no pain (5.6% vs. 7.9% and 5.3% vs. 7.4% of the total daily activity, respectively; both Cohen's D=0.33, p=0.001; Figure 2). Daily activity counts and light activity, in contrast, did not reveal significant differences (Figure 2). Calculating bout minutes of moderate/vigorous activity only did not improve the discrimination compared with moderate/vigorous activity (Freedson: Cohen's D=0.31, p=0.009; Troiano: Cohen's D=0.30, p=0.011 [ANCOVA]). Accelerometer parameters determined according to Swartz did not show significant differences between any of the pain strata. Despite these statistically significant findings, accelerometry did not attain the discriminatory ability of the CST for non-acceptable pain vs. no pain (Cohen's D=0.61, p<0.001). Moreover, the CST - unlike accelerometry - was also able to discriminate between moderate pain and no pain (Cohen's D = 0.49, p<0.001).

**Conclusions:** Amongst physical activity parameters calculated from accelerometry, moderate/vigorous activity as defined by Freedson and Troiano was most sensitive in discriminating between participants with non-acceptable vs. no knee pain. Light activity, and minutes of activity

**Figure 1** Accelerometer cutpoints to assess intensity of physical activity, based on definitions from three different authors

| Physical activity intensity levels ↓ | Minute Cut Points for each author | | |
|---|---|---|---|
| | Swartz | Freedson | Troiano |
| Light (1.5 to < 3 METs) | 100-573 | 100-1951 | 100- 2019 |
| Moderate (3 to 6 METs) | 574-4944 | 1952-5724 | 2020-5998 |
| Vigorous or greater (≥ 6 METs) | 4945+ | 5725 + | 5999+ |

MET=metabolic equivalent of task (measure of energy expenditure)

**Figure 2** Discrimination between knee pain strata for the Chair Stand Test (CST) and 10 accelerometer parameters (average daily counts & minutes of activity). Threshold definitions (Def.) from different authors are indicated by letters S (Swartz), F (Freedson), T (Troiano)

| Knee Pain Strata ↓ | Def. → | Daily CTs (x 1000) | Light Activity (min) | | | Moderate vigorous activity (min) | | | Bouts of Moderate vigorous activity (min) | | | CST (s) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | S | F | T | S | F | T | S | F | T | |
| NRS 0 n = 244 | Mean (SD) | 232 (113) | 181 (45) | 278 (75) | 279 (75) | 121 (58) | 24 (22) | 22 (21) | 48 (43) | 12 (16) | 11 (15) | 9.4 (2.5) |
| NRS 1/2 n = 106 | Mean (SD) | 255 (138) | 173 (40) | 273 (68) | 275 (68) | 128 (56) | 28 (26) | 27 (25) | 53 (48) | 15 (18) | 14 (18) | 9.4 (2.1) |
| | CD | 0.20 | 0.18 | 0.06 | 0.06 | 0.14 | 0.19 | 0.20 | 0.12 | 0.16 | 0.17 | 0.01 |
| NRS 3/4 n = 103 | Mean (SD) | 238 (122) | 183 (48) | 290 (77) | 292 (78) | 129 (61) | 22 (20) | 21 (19) | 51 (47) | 10 (13) | 9 (13) | 10.7*** (3.4) |
| | CD | 0.06 | 0.05 | 0.17 | 0.17 | 0.15 | 0.07 | 0.08 | 0.7 | 0.15 | 0.14 | 0.49 |
| NRS >4 n = 99 | Mean (SD) | 210 (99) | 185 (44) | 284 (82) | 285 (83) | 116 (59) | 17** (17) | 16** (17) | 43 (41) | 7** (13) | 7* (13) | 10.9*** (3.3) |
| | CD | 0.19 | 0.09 | 0.08 | 0.08 | 0.07 | 0.33 | 0.33 | 0.11 | 0.31 | 0.30 | 0.61 |

CTs=counts; CD=Cohen's D related to NRS 0; bout=8 out of 10-minute period with an intensity ≥ the threshold

* p< 0.05; ** p < 0.01; *** p < 0.001 compared with NRS 0 (with adjustment for age and BMI)

as defined by Swartz, in contrast, did not differ between pain strata. Yet, accelerometry parameters were not capable of discriminating between different knee pain levels as did the CST. Therefore, the CST can be recommended for the use in clinical studies that attempt to monitor improvements in pain and function, with further innovations in accelerometry and its technical analysis being required.

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## POSTOPERATIVE OUTCOME OF PATIENTS WHO UNDERWENT TOTAL JOINT REPLACEMENT DURING THE TANEZUMAB PHASE 3 OSTEOARTHRITIS DEVELOPMENT PROGRAM: A 24-WEEK OBSERVATIONAL STUDY

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**Purpose:** Tanezumab, a monoclonal antibody against nerve growth factor, is in development for the treatment of osteoarthritis (OA). The aim of this study was to evaluate the postoperative outcome of patients who had undergone a total joint replacement (TJR) while participating in one of three parent tanezumab phase 3 OA studies.
**Methods:** This phase 3 observational study (NCT02674386) followed consenting patients from three phase 3 randomized controlled trials, who underwent TJR (knee, hip, or shoulder) at any time (during the parent study treatment period or safety follow up period), for 24 weeks after surgery. Endpoints included: Surgeon's Assessment of Procedural Difficulty (uneventful, minor complications, major complications) at the time of TJR; post-surgical complications (clinically significant events attributable to the TJR, derived from adverse events) up to Week 24; additional or corrective procedures (procedures or investigations related to the TJR) up to Week 24; and patient's overall satisfaction with the result of surgery (based on the question 'How satisfied are you with the results of your surgery?'; somewhat satisfied, very satisfied, somewhat dissatisfied, or very dissatisfied) at Week 24. Patients were contacted by telephone (to collect information on adverse events and planned further procedures) and at prespecified time points they completed questionnaires. An external Adjudication Committee utilized clinical study data and magnetic resonance images/radiographs to determine in a blinded and independent fashion the presence of: primary osteonecrosis, rapidly progressive OA (RPOA) type 1 (rapid loss of joint space width $\geq$ 2mm within a year) or type 2 (abnormal bone loss/joint destruction), normal progression of OA (NPOA), subchondral insufficiency fracture, pathological fracture, other joint outcome, or not enough information to differentiate RPOA vs NPOA or specify a diagnosis.
**Results:** Of 258 patients with a TJR, 154 (59.7%) consented and were enrolled in the current study; data from 150 patients with 169 TJRs (99 knees [58.6%], 69 hips [40.8%], and 1 shoulder [0.6%]) were eligible for evaluation. At baseline in the parent studies 91.1% [154/169] of the joints were Kellgren-Lawrence radiographic severity grade 3 or 4. In the parent studies the patients received placebo (n=20), tanezumab 2.5 mg (n=52), tanezumab 5 mg (n=53), tanezumab 2.5 mg titrated to 5 mg (tanezumab 2.5/5 mg, n=8), or a nonsteroidal anti-inflammatory drug (NSAID; n=17). The TJR was performed 299 days (mean) from randomization in the parent studies. Based on the joint with the worst adjudicated outcome, the 150 patients were adjudicated to have osteonecrosis (n=1), RPOA type 1 (n=3), RPOA type 2 (n=8), NPOA (n=130), other joint outcome (n=6), or not enough information to determine RPOA vs NPOA (n=2). A total of 95.1% (116/122) of patients had Surgeon's Assessment of Procedural Difficulty ratings of uneventful and none had major complications. Of 6 patients with procedural difficulty ratings of minor complications, 4 had hip TJRs which were adjudicated as NPOA (tanezumab 2.5 mg n=1, tanezumab 5 mg n=1) or RPOA type 2 (tanezumab 5 mg n=2) and 2 had knee TJRs (both adjudicated as NPOA, tanezumab 5 mg). The minor complications included difficulty removing the head of the joint, abnormal bone appearance, osteosclerosis, capsule stenosis, and accumulation of synovial fluid. Through the 24-week study, 4.0% (6/150) of patients had post-surgical complications (5 hip TJRs and 1 knee TJR, all adjudicated as NPOA: tanezumab 2.5 mg n=2, tanezumab 5 mg n=4). These included: hematoma/periprosthetic fracture/hip infection; incision site infection; luxation of prosthesis joint; anemia; and periprosthetic infection/hip dislocation. A total of 6.7% (10/150) of patients required additional or corrective procedure(s) (6 hip TJRs and 4 knee TJRs, adjudicated as NPOA [n=9] or RPOA type 2 [n=1]: tanezumab 2.5 mg n=3, tanezumab 5 mg n=6, NSAID n=1), including: fracture treatment/hematoma evacuation/surgery; joint debridement, manipulation or fluid drainage; device repositioning; tendon repair; and imaging. At Week 24, 6.1% (8/131) of patients were somewhat dissatisfied or very dissatisfied with the result of the surgery (2 hip TJRs and 6 knee TJRs, adjudicated as NPOA [n=7] or other joint outcome [n=1]: placebo n=1, tanezumab 2.5 mg n=4, tanezumab 5 mg n=2, NSAID n=1).
**Conclusions:** Procedural difficulty of minor complications during surgery, post-surgical complications, and additional or corrective procedures were infrequent, but occurred primarily in patients treated with tanezumab in the parent studies, and more frequently with tanezumab 5 mg than tanezumab 2.5 mg. Most of these cases were adjudicated as NPOA. The TJR outcomes in the patients with RPOA were similar to NPOA. Few patients were dissatisfied with their TJR, most of them were previously treated with tanezumab.

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## CAN THE INDIVIDUAL PATIENT OUTCOME FOLLOWING PATIENT EDUCATION AND EXERCISE THERAPY BE PREDICTED? - A PROGNOSTIC MODEL STUDY INCLUDING 6,767 PATIENTS WITH KNEE OSTEOARTHRITIS FROM THE DANISH GLA:D® REGISTRY

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**Purpose:** Exercise therapy in combination with patient education is universally recommended as first line treatment for patients with knee osteoarthritis (OA), but underutilised. One reason might be, that patients find average benefits difficult to relate to and would prefer information on the importance and benefits of exercise therapy for patients with similar characteristics as themselves. Another reason might be that medical doctors lack experience or time to discuss exercise therapy as a treatment option. To support the decision process in patients with symptomatic knee OA, we aimed to build a calculator, consisting of three models predicting the individual change in pain intensity, quality of life and walking speed immediately after an 8-week patient education and exercise therapy program.
**Methods:** We used data from patients with knee OA from the 'Good Life with Osteoarthritis in Denmark' (GLA:D®) registry. Patients participated in a program consisting of two educational and 12 physiotherapist-supervised exercise therapy sessions (one hour twice weekly for six weeks). Patients were included if they provided baseline information on 51 characteristics (binary and continuous) and follow-up data at 3 months for change in 1) pain intensity measured on a VAS scale (0-100, best to worst), 2) quality of life (QOL) measured by the