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Who are likely to benefit from the Good Life with osteoArthritis in Denmark (GLAD) exercise and education program? An effect modifier analysis of a randomised controlled trial

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Objective: To identify contextual factors that modify the treatment effect of the ‘Good Life with osteoArthritis in Denmark’ (GLAD) exercise and education programme compared to open-label placebo (OLP) on knee pain in individuals with knee osteoarthritis (OA).

Methods: Secondary effect modifier analysis of a randomised controlled trial. 206 participants with symptomatic and radiographic knee OA were randomised to either the 8-week GLAD programme (n = 102) or OLP given as 4 intra-articular saline injections over 8 weeks (n = 104). The primary outcome was change from baseline to week 9 in the Knee injury and Osteoarthritis Outcome Score questionnaire (KOOS) pain subscale (range 0 (worst) to 100 (best)). Subgroups were created based on baseline information: BMI, swollen study knee, bilateral radiographic knee OA, sports participation as a young adult, sex, median age, a priori treatment preference, regular use of analgesics (NSAIDs or paracetamol), radiographic disease severity, and presence of constant or intermittent pain.

Results: Participants who reported use of analgesics at baseline seem to benefit from the GLAD programme over OLP (subgroup contrast: 10.3 KOOS pain points (95% CI 3.0 to 17.6)). Participants with constant pain at baseline also seem to benefit from GLAD over OLP (subgroup contrast: 10.0 points (95% CI 2.8 to 17.2)).

Conclusions: These results imply that patients who take analgesics or report constant knee pain, GLAD seems to yield clinically relevant benefits on knee pain when compared to OLP. The results support a stratified recommendation of GLAD as management of knee OA.

Trial registration: ClinicalTrials.gov Identifier: NCT03843931. EudraCT number 2019-000809-71.

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Introduction

Patient education and exercise programmes are recommended as a first choice management strategy for knee osteoarthritis (OA) due to beneficial effects in several randomised controlled trials (RCTs) with no-attention control groups. The ‘Good Life with osteoArthritis in Denmark’ programme (GLAD) is a standardised framework of patient education and exercise being implemented in several countries worldwide. However, our recent RCT comparing the GLAD programme to open-label placebo (OLP) in 206 people with knee OA (the DISCO trial) showed equivocal improvements in knee pain and other important OA outcomes in both groups with no group differences, raising questions about the true effect of GLAD on knee OA symptoms.

Failure of the GLAD programme to confer additional symptomatic benefit over OLP at a group level may be due to population...
heterogeneity and large variation in the responses to the intervention. Evaluation of factors that may predict differential treatment response to GLAD vs OLP becomes more pressing when the two treatments have comparable effectiveness (i.e., equivalent) in a randomised trial\(^1\). Our results create an intense need for moving from targeting all people with knee OA to identifying subgroups who may benefit (i.e., stratified medicine) from GLAD. Stratified medicine refers to the targeting of treatments according to the biological or risk characteristics shared by subgroups of patients\(^1\). The European League Against Rheumatism (EULAR) clinical guidelines have identified moderators of knee OA outcomes as an important research priority to optimize individualized treatment\(^1\).

A registry-based cohort study from the GLAD registry in Denmark (>6,700 patients) explored 51 patient characteristics as predictors of changes in knee OA pain following the GLAD programme but did not identify any relevant predictors\(^1\). However, registry-based cohort studies are prone to bias and a more valid method for identifying effect modifiers is through secondary analyses of RCT data as the RCT allows for causal effect estimations\(^8\) and less biased exploration of effect modifiers\(^1\). Our recent RCT\(^7\) is the only RCT of the GLAD programme that has been conducted and secondary exploration of effect modifiers has not been done before.

Potential contextual factors that may modify the treatment may be selected based on prior research and/or the plausibility of hypothesised effects. For instance, age, Body Mass Index (BMI), and disease severity are often considered potential effect modifiers and used as randomisation stratification factors in clinical trials to balance prognostic factors in RCTs. Furthermore, knee swelling, the patients’ habitual use of analgesics, pain characteristics, previous experience with physical activity or exercise could also impact the effectiveness of exercise and education in a knee OA population. Also, the participants’ treatment preferences may influence the outcome of the treatment they are randomly allocated to\(^10\) – particularly in open-label and unblinded study designs, which is the typical design used in non-pharmacological OA research.

Consequently, the aim was to identify contextual factors that modify the treatment effect of GLAD on pain compared to that of OLP in individuals with knee OA using data from our recent RCT\(^7\).

**Methods**

**Trial design**

The trial was an open-label, single-centre RCT with two parallel intervention groups (1:1 allocation ratio) comparing the GLAD exercise and education programme with OLP in the form of 4 intra-articular saline injections, each separated by 2 weeks. The primary endpoint was assessed at week 9 (9 weeks after initiation of treatment)\(^1\). The study was approved by the Health Research Ethics Committee for the Capital Region of Denmark (H-19012472) and the protocol was registered prospectively at [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) (NCT03843931) on the 18th of February, 2019 and the results of the primary analyses have been published\(^1\).

**Participants**

Between 30th July 2019 and 17th September 2020, we recruited participants from the OA outpatients clinic at Bispebjerg-Frederiksberg Hospital in Copenhagen. All participants provided written informed consent before participation.

Inclusion criteria were >50 years of age, a BMI ≤35 kg/m\(^2\), knee OA according to the American College of Rheumatology classification criteria\(^12\), average knee pain during weight-bearing activities in the last week of at >4 on an 11 point scale (0 = no pain; 10 = worst possible pain), and radiographically verified tibiofemoral OA (Kellgren–Lawrence (K-L) grade of ≥2 or more\(^13\)). The main exclusion criteria were intra-articular treatments of any kind in either knee or participation in therapeutic exercise within 3 months of the baseline visit. Details of the inclusion and exclusion criteria are provided in the published protocol\(^1\).

Potential participants were informed about the trial during a visit to the OA outpatients clinic. The information was delivered neutrally, ensuring that the descriptions of GLAD and OLP were promoted equally. Clinical equipoise was emphasised by stating that the investigators had no treatment preference\(^1\). The OLP (saline injections) was described as in principle being an inert substance but with potential symptomatic benefits comparable to GLAD (exercise and education)\(^9\). The participants were informed that mechanisms of action in both treatments are unclear and probably involve the sum and interaction of many factors\(^1\). The most symptomatic knee at baseline was chosen as the study knee.

**Interventions**

Full details of the interventions are in the published protocol\(^1\) and main trial report\(^1\). In brief, GLAD is an 8-week structured treatment programme for people with symptomatic knee or hip OA consisting of two 1.5 h patient education sessions and twelve 1-h supervised neuromuscular exercise sessions delivered by GLAD certified physiotherapists\(^3\). The two educational sessions were offered once weekly over 2 weeks and presented knowledge about knee OA, various treatment options with a focus on exercise and its benefits, and advice about self-management\(^4\). The exercise sessions were delivered twice weekly for 6 weeks as group-based, supervised sessions. The complete GLAD programme was scheduled to last 8 weeks from the baseline visit and was delivered at the department of physiotherapy at Bispebjerg-Frederiksberg Hospital in Copenhagen, Denmark.

OLP was delivered as 4 ultrasound-guided\(^14\) intra-articular injections of 5 mL isotonic solution of sodium chloride in sterile water (0.9% = 9 mg/mL) into the study knee. The injections were offered at weeks 1, 3, 5, and 7 after baseline. The injections were given without local analgesics. Excessive joint fluid was aspirated before injection if deemed clinically relevant.

**Randomisation and blinding**

Demographic information and all baseline measures were recorded before randomisation. Participants were allocated to either the GLAD programme or OLP based on a computer-generated randomisation list with permuted random blocks of variable size (2–6 in each block) generated before enrolment of participants. The randomisation list was developed by a biostatistician (RC) who had no interaction with the participants. The allocation was equal (1:1 ratio) stratified by four baseline conditions: BMI ≥30 kg/m\(^2\), swollen study knee upon palpation\(^15\), bilateral radiographic tibiofemoral OA (K-L grade ≥2 in both knees), and sports participation as a young adult (20ies). The individual allocation was concealed until a participant had completed baseline assessments and an investigator pressed ‘randomise’ in the electronic trial management system.

As this was an open-label trial, neither the participants nor health professionals delivering the interventions were blinded to treatment allocation after randomisation.
Primary outcome

The primary outcome was the change from baseline to week 9 (end of treatment) in the Knee injury and Osteoarthritis Outcome Score questionnaire (KOOS) pain subscale related to the study knee\(^{16,17}\). The KOOS pain subscale consists of 9 questions related to knee pain with the previous week as the period considered when answering the questions. Standardised answer options are given (5 Likert boxes) and each question is assigned a score from 0 to 4 (best to worst). A normalised 0–100 score (0 indicating extreme symptoms and 100 indicating no symptoms) is calculated. The participants were requested not to use any analgesics for 48 h before all assessments, including the KOOS pain assessment\(^11\). A minimal clinically relevant between group difference of 8 points has been suggested by the inventors of the questionnaire\(^18\).

Potential effect modifiers

A priori we identified a range of baseline variables to be explored as potential effect modifiers and used to create subgroups: Firstly, we re-used the factors used for the stratified randomisation\(^11\): BMI \(>30\) kg/m\(^2\), swollen study knee upon palpation\(^15\), bilateral radiographic tibiofemoral OA (K-L grade \(\geq 2\) in both knees), and sports participation as a young adult (20ies). Further, sub-groupings were done according to the participants’ biological sex (male/female), and on an arbitrary older age subgroup using the median age (\(>68.7\) years). The presence/absence of swelling in the study knee at baseline was assessed by a medical doctor based on presence/absence of palpable effusion\(^15\). Study knee radiographic disease severity subgroups were created using the unilateral study knee K-L grade cut off at 3.5 (comparing grades 2—3 vs grade 4). Regular use of analgesics (paracetamol and NSAIDs) at baseline was recorded (yes/no) during an interview with an investigator. Absence/presence of constant pain was defined as a score of 0 or \(>0\), respectively, on the constant pain subscore of the Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire\(^19\). Likewise, absence/presence of intermittent pain was defined as a score of 0 or \(>0\), respectively, on the intermittent pain ICOAP subscore\(^19\). Finally, the participants were classified according to their a priori preference for the two treatments determined at inclusion (before randomisation). The preference did not affect the subsequent random allocation, which the participants were informed about. The participants were asked which of the interventions they would prefer if they could choose. The participants could choose between ‘GLAD’, ‘Saline’, or ‘Indifferent’. For the present analyses, participants who answered ‘Indifferent’ were ignored. The potential effect modifiers are summarised in Table I.

Sample size and power considerations

The original sample size was calculated for testing equivalence of the two treatments in the primary analysis and 206 participants

<table>
<thead>
<tr>
<th>Potential effect modifiers</th>
<th>Description</th>
<th>Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or overweight vs Obesity*</td>
<td>The participants’ bodymass index (BMI; kg/m(^2))</td>
<td>0 = BMI &lt;30 kg/m(^2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = BMI (\geq 30) kg/m(^2)</td>
</tr>
<tr>
<td>Swollen Study Knee*</td>
<td>Assessed by a medical doctor for palpable presence of swelling (yes/no).</td>
<td>0 = Not swollen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = Swollen</td>
</tr>
<tr>
<td>Bilateral radiographic tibiofemoral OA*</td>
<td>Kellgren—Lawrence (K-L) grading of bilateral knee radiographs.</td>
<td>0 = K-L grade (\geq 2) in both knees</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = K-L grade (\geq 2) in both knees</td>
</tr>
<tr>
<td>Active as young adult*</td>
<td>Baseline question: &quot;When you were in your 20yes did you participate in sports activities for at least 1 h 2 times or more per week?&quot;;</td>
<td>0 = No</td>
</tr>
<tr>
<td></td>
<td>Female or male biologic sex</td>
<td>1 = Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = Female</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = Male</td>
</tr>
<tr>
<td>Age — median cutoff</td>
<td>Age at inclusion in the trial. Cut-off at median (68.75 years).</td>
<td>0 = Younger than 68.75 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = Older than 68.75 years</td>
</tr>
<tr>
<td>Preference</td>
<td>At inclusion (before randomisation), the participants were asked which of the study treatments they would prefer if they could choose. The preference did not affect the random allocation. The participants could choose between ‘GLAD’, ‘Saline’, or ‘Indifferent’.</td>
<td>0 = Saline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = GLAD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>‘Indifferent’ are ignored, i.e., left out of the analyses</td>
</tr>
<tr>
<td>Analgesics use</td>
<td>Interview regarding use of paracetamol or NSAIDs for their knee OA pain.</td>
<td>0 = Did not use analgescis</td>
</tr>
<tr>
<td></td>
<td>Specific type and dose were not recorded.</td>
<td>1 = Did use analgescis</td>
</tr>
<tr>
<td>Radiographic disease severity</td>
<td>Kellgren—Lawrence (K-L) grading of radiograph of study knee.</td>
<td>0 = K-L grade (\geq 2) or 3</td>
</tr>
<tr>
<td>Constant knee pain</td>
<td>Note: A grade (\geq 2) was an inclusion criterion.</td>
<td>1 = K-L grade (\geq 4)</td>
</tr>
<tr>
<td></td>
<td>Based on the Constant pain subscale of the Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire.</td>
<td>0 = No constant knee pain (constant pain score &lt; 1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = Constant knee pain (constant pain score (\geq 1))</td>
</tr>
<tr>
<td>Intermittent knee pain</td>
<td>Based on the Intermittent pain subscale of the Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire.</td>
<td>0 = No intermittent knee pain (intermittent pain score &lt; 0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = Intermittent knee pain (intermittent pain score (\geq 0))</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, Body Mass Index; ICOAP, Intermittent and Constant Osteoarthritis Pain; TF, Tibio Femoral.

* These variables were part of the stratified randomisation.

Table I

Baseline variables selected for exploration of possible effect modification
were included\(^1\). There was no sample size calculation for the present secondary analysis but the original sample size calculation did estimate that 114 participants provided adequate power (80.4\%) to detect clinically relevant group differences in the primary outcome (i.e., 8 KOOS pain points)\(^1\), which mitigates the sample size problem to some extent. Nevertheless, the study was not designed for these secondary analyses and hence the test of interactions may be underpowered. The power for detecting an interaction depends on the size of the interaction relative to the overall treatment effect, however, if these are of the same magnitude, then about four times the sample size needed to detect an overall effect will be needed to reliably detect an interaction\(^2\). On the other hand, since we are testing many baseline variables, the risk of observing statistically significant interactions by chance will increase\(^3\). Hence, the risks of both false-negative results from lack of power and false-positive results are increased. The statistical significance of the treatment effect in individual subgroups will not be reported, as the risk of false-negative and false-positive results are very high\(^4\).

**Statistical analysis**

These secondary statistical analyses were performed according to an a priori statistical analysis plan that was written, closed, and signed before the analyses were commenced (Appendix 1). The analyses focused on the primary outcome; the change from baseline in the KOOS pain subscale at week 9. The analyses were performed using the intention-to-treat population consisting of all randomised participants. Missing data at week 9 were conservatively replaced with the baseline observation (i.e., non-responder imputation).

For the analyses of whether the dichotomous baseline variables modify the treatment effect, analysis of covariance models were used with group (GLAD vs OLP) and the moderator (with 2 levels) as main effects together with their interaction and the baseline KOOS pain value as covariate. From these models, any group difference in the change from baseline in KOOS pain between subgroups of participants based on the presence of the potential effect modifiers were estimated together with the associated 95\% confidence interval (and the \(P\)-value) corresponding to the test of the hypothesis of no interaction between group and treatment modifier. For the analyses of the main trial\(^1\) we applied repeated measures mixed linear models with adjustment for stratification factors. To simplify and facilitate interpretation\(^5\), we have applied a simpler and more conservative statistical approach to this study\(^6\).

To assess the robustness of the results, we repeated the analyses on the As-Observed population consisting of all participants for whom data have been observed with no imputation of missing data.

In our a priori statistical analysis plan, we had planned to analyse the association between a number of continuous baseline variables with the primary outcome using linear regression models. However, none of the regression models fitted the data satisfactorily (i.e., not evenly distributed vertically, too many outliers, and with clear patterns, as well as lack of linearity), neither as raw nor transformed data sets, and hence these models were abandoned.

All analyses were performed using the statistical software SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

**Patient involvement**

Two patient research partners (1 female, 1 male) were involved in the process of designing and preparing the parent RCT, but not in the design, planning, interpretation, or reporting of the current secondary analyses.

**Results**

**Participants**

Between 30th July 2019 and 17th September 2020, a total of 317 individuals were screened clinically for eligibility, of which 206 subjects were randomised: 102 to the GLAD group, and 104 to the OLP group (Fig. 1). Baseline characteristics were similar in the two groups (Table II).

**Overall effect**

The mean changes in KOOS pain score from baseline to week 9 were 8.5 points (SE 1.3) in the GLAD group and 6.7 points (SE 1.3) in the OLP group with a group difference of 1.8 points (95\% confidence interval, −1.8 to 5.4; \(P = 0.32\)). The overall effect is similar to that from the main trial\(^7\).

**Effect modifiers**

The results of the subgroup analyses are summarised in Fig. 2. There was a statistically significant difference between subgroups of 10.3 KOOS pain points (95\% CI 3.0 to 17.6; \(P = 0.006\)) favouring the GLAD programme among participants who used analgesics (NSAIDS or paracetamol) at baseline (\(n = 77\)) compared to participants who did not use analgesics at baseline (\(n = 129\)).

When comparing participants who at baseline reported to have constant knee pain (\(n = 82\)), with those who reported not to have constant pain (\(n = 124\)), there was a statistically significant difference between subgroups in favour of the GLAD programme of 10.0 KOOS pain points (95\% CI 2.8 to 17.2; \(P = 0.007\)) indicating superiority of the GLAD programme over OLP among participants with constant baseline knee pain.

Relatedly, participants without intermittent pain at baseline (\(n = 19\)) seem to benefit from GLAD, when compared to participants with intermittent baseline pain (\(n = 187\)), although the estimated subgroup difference is imprecise based on the width of the confidence interval (mean subgroup difference: −11.3 (95\% CI −24.2 to 1.6; \(P = 0.086\)) leaving the results inconclusive.

Finally, the participants’ preference for the study treatments (GLAD vs OLP) seems to moderate the treatment effect, so that participants who prefer GLAD have a greater benefit when receiving GLAD (Fig. 2), albeit the subgroup contrast estimate is imprecise based on the width of the confidence interval (mean subgroup difference −7.9 KOOS pain points (95\% CI −16.2 to 0.5; \(P = 0.064\)). The remaining potential effect modifier variables did not seem to moderate the treatment effect, although some of the subgroup differences are imprecisely estimated (Fig. 2).

On a post hoc level, we assessed if the subgroups reporting use of analgesics at baseline, constant knee pain, GLAD preference, and no intermittent knee pain included the same participants. Of the 77 participants reporting use of analgesics, 36 (47\%) reported constant knee pain at baseline and 28 (36\%) had GLAD as their treatment preference, showing only a partial overlap between subgroups. Also, of the 82 participants reporting constant baseline pain 24 (29\%) had GLAD as treatment preference. Of the 19 participants reporting no intermittent pain 16 (84\%) also reported constant pain and 9 (12\%) used analgesics. A graphical illustration of selected subpopulations and their overlap is in Fig. 3.

We further explored if the participants who took analgesics at baseline had more severe baseline pain assessed as the KOOS pain subscale and the baseline ICOAP constant pain score. Participants who at baseline used analgesics (\(n = 77\)) had a mean baseline KOOS Pain score of 54.4 points (SE 1.6), whereas participants who did not use analgesics at baseline (\(n = 129\)) had a mean baseline score of...
58.3 points (SE 1.2). The mean difference was 3.9 points (95% CI -0.1 to 7.9; \( P = 0.053 \)). Among baseline analgesic users and non-users, the baseline ICOAP constant scores were 25.2 points (SE 3.0) and 16.3 points (SE 2.3), respectively, with a mean difference of 8.9 points (95% CI 1.5 to 16.3; \( P = 0.018 \)).

Finally, we sub-grouped the participants based on having constant baseline pain (ICOAP constant score >0) and not having intermittent baseline pain (ICOAP intermittent score = 0). Only 16 participants had constant pain and no intermittent pain at baseline (\( n = 16; 11 \text{ GLAD/}5 \text{ OLP} \)) resulting in a very imprecise estimated
The parent RCT showed equivalent improvements in knee pain following GLAD and OLP, which raises important questions about the effect of GLAD as a one-size-fits-all strategy for knee OA. A previous study from the GLAD registry explored a large number of patient characteristics, but no relevant predictors better than the overall average effect were identified\(^1\). However, the study was observational and lacked a control group to contrast treatment responses against, which may explain why no factors were identified. In contrast, our results were based on a randomised comparison with an OLP, providing a more valid and less biased platform for identification of effect modifiers.

The underlying mechanisms of the differential response to GLAD vs OLP between analgesics users and non-users are not possible to identify from this study but need to be investigated in future studies. It could be speculated that the patient education increased the participants’ knowledge about OA and thereby altering their use of analgesics. The analgesics users reported on average 3.9 points higher baseline KOOS pain scores than non-users, which does not constitute a clinically relevant difference (suggested to be 8–10 points), and hence the differential response to GLAD vs OLP is likely not owing to differences in the baseline KOOS pain score. Also, the difference in baseline ICOAP scores did not exceed the minimal clinically important difference of 18 points\(^2\). Unfortunately, we do not know the dose or the frequency of the analgesics used, however, the data was collected as part of an interview with a medical doctor and the simplicity of the variable (use/non-use restricted to NSAIDs or paracetamol) makes it feasible to include in a clinical decision making.

The finding that GLAD could be superior to OLP among participants who report constant baseline pain (vs those that do not have constant baseline pain) is supported by a similar association among the participants who did not report intermittent pain, and further by the post hoc analysis of participants with constant and no intermittent pain. Again, the underlying mechanisms are not possible to assess from the present study, but is has been suggested that individuals with variable pain are more likely to exhibit large placebo responses\(^3\). A previous study has highlighted that it is unknown if constant or intermittent pain is more severe\(^4\), but our results suggest that analgesics users report slightly higher ICOAP constant pain scores, although not above the minimal clinically important difference. The subgroups based on analgesics usage and the presence of constant pain are not the same (Fig. 3), again suggesting that the baseline pain intensity is not the underlying mechanism. It is important to note that the current results do not imply that actively targeting the subgroup factor (analgesics usage or presence of constant pain) could make GLAD even more effective, but rather indicate that the presence of these factors at baseline may increase the chance of benefitting from GLAD. Regarding the clinical feasibility of identifying the constant pain subgroup, the implementation of simple screening questions related to the presence of constant knee pain is easy to implement in clinical practice.

Our results also suggest that patients who prefer GLAD may experience higher efficacy. This result is in line with a meta-analysis of preference studies in musculoskeletal conditions that showed that patients’ preferences do affect treatment outcomes in RCTs\(^5\), which is also supported by a meta-analysis of randomised preference trials\(^6\). Hence it is important to explore a patient’s preference for the GLAD program before referring and our results support the concept of shared decision making. It could be

### Discussion

In this secondary effect modifier analysis of an RCT, we aimed to identify baseline factors that could modify the effect of GLAD on pain compared to that of OLP in patients with knee OA. Our results show that patients who either take analgesics report constant pain, and who prefer the GLAD program seem to benefit more from GLAD than from OLP. The identification of these patient subgroups is very feasible in a clinical setting as they rely on a short interview related to analgesics use, a signalling question about presence of constant pain (or based on the constant pain subscale of the ICOAP questionnaire), and the patients’ preference for engaging in a GLAD program.

This is the first study to identify treatment modifiers of GLAD. The parent RCT showed equivalent improvements in knee pain following GLAD and OLP\(^7\), which raises important questions about the effect of GLAD as a one-size-fits-all strategy for knee OA. A previous study from the GLAD registry explored a large number of patient characteristics, but no relevant predictors better than the overall average effect were identified\(^1\). However, the study was observational and lacked a control group to contrast treatment responses against, which may explain why no factors were identified. In contrast, our results were based on a randomised comparison with an OLP, providing a more valid and less biased platform for identification of effect modifiers.

The underlying mechanisms of the differential response to GLAD vs OLP between analgesics users and non-users are not possible to identify from this study but need to be investigated in future studies. It could be speculated that the patient education increased the participants’ knowledge about OA and thereby altering their use of analgesics. The analgesics users reported on average 3.9 points higher baseline KOOS pain scores than non-users, which does not constitute a clinically relevant difference (suggested to be 8–10 points), and hence the differential response to GLAD vs OLP is likely not owing to differences in the baseline KOOS pain score. Also, the difference in baseline ICOAP scores did not exceed the minimal clinically important difference of 18 points\(^2\). Unfortunately, we do not know the dose or the frequency of the analgesics used, however, the data was collected as part of an interview with a medical doctor and the simplicity of the variable (use/non-use restricted to NSAIDs or paracetamol) makes it feasible to include in a clinical decision making.

The finding that GLAD could be superior to OLP among participants who report constant baseline pain (vs those that do not have constant baseline pain) is supported by a similar association among the participants who did not report intermittent pain, and further by the post hoc analysis of participants with constant and no intermittent pain. Again, the underlying mechanisms are not possible to assess from the present study, but is has been suggested that individuals with variable pain are more likely to exhibit large placebo responses\(^3\). A previous study has highlighted that it is unknown if constant or intermittent pain is more severe\(^4\), but our results suggest that analgesics users report slightly higher ICOAP constant pain scores, although not above the minimal clinically important difference. The subgroups based on analgesics usage and the presence of constant pain are not the same (Fig. 3), again suggesting that the baseline pain intensity is not the underlying mechanism. It is important to note that the current results do not imply that actively targeting the subgroup factor (analgesics usage or presence of constant pain) could make GLAD even more effective, but rather indicate that the presence of these factors at baseline may increase the chance of benefitting from GLAD. Regarding the clinical feasibility of identifying the constant pain subgroup, the implementation of simple screening questions related to the presence of constant knee pain is easy to implement in clinical practice.

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**Table II**

**Baseline values in the ITT population**

<table>
<thead>
<tr>
<th>Treatment preference</th>
<th>GLAD, n(%)</th>
<th>Open-label placebo, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLAD</td>
<td>37 (36.3%)</td>
<td>27 (26%)</td>
</tr>
<tr>
<td>IA Saline</td>
<td>33 (32.4%)</td>
<td>46 (44.2%)</td>
</tr>
<tr>
<td>Indifferent, n(%)</td>
<td>24 (23.5%)</td>
<td>26 (25%)</td>
</tr>
</tbody>
</table>

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Unless otherwise indicated, data are expressed as mean (SD). The percentages have been rounded and may not total 100.

**BM:** Body Mass Index; **K/L:** Kellgren–Lawrence; **ICOAP:** Intermittent and Constant Osteoarthritis Pain; **OA:** osteoarthritis.

* Primary outcome measure.

\(^1\) Missing data from 13 participants (GLAD 8, IA Saline 5).

\(^2\) Grades on the Kellgren–Lawrence scale range from 0 to 4, with a grade of 2, 3, or 4 indicating definite osteoarthritis and higher grade indicating more severe disease.
speculated that differential placebo responses prompted by match/mismatch between preference and actual allocation could contribute to the difference.

Our study has some limitations. Despite being based on a large clinical trial, the interaction tests have reduced statistical power, were repeated for multiple baseline characteristics, and are imprecise, especially in some of the subgroups with low prevalence (e.g., bilateral OA and intermittent knee pain). Hence, increased risk of both false-negative and false-positive results may be present. The precision of the estimates generally includes clinically irrelevant subgroup differences and hence there is no guarantee of significant benefits for all patients in the identified subgroups. The combination of the regular use of analgesics (NSAIDs and paracetamol) into a single category for subgroup analysis may be too crude as NSAIDs and paracetamol may not have the same effect modification. Further, our study does not provide any guidance for patients who do not use analgesics or do not have constant pain but are limited to a suggestion that these patients seem to benefit less from GLAD, and hence other treatment options could be considered. Unfortunately, the efficacy of alternatives has not been documented in patients not using analgesics or with intermittent pain but should be a focus for future research. Also, some contextual factors are more context specific than others, and the effect modifiers of GLAD vs OLP may be different in other clinical settings.

There are also strengths to our study, including the robust parent trial with a rigorous trial design and conduct. At inclusion both interventions were promoted in equal and neutral terms to reduce any bias associated with favourable notions about either intervention. The primary analysis used a conservative imputation of missing data and the results are robust to sensitivity analyses. The baseline characteristics to be investigated were predefined, and all interaction test results are reported, in contrast to most reports on subgroup analyses. Finally, the identified treatment modifiers are easy to implement in clinical practice and can be used to make informed and shared decision making about referral to GLAD as conservative management of knee OA.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of patients (GLAD/OLP)</th>
<th>GLAD Mean (SE)</th>
<th>OLP Mean (SE)</th>
<th>Mean Difference</th>
<th>Contrasts within subgroups Mean diff. (95% CI)</th>
<th>Contrasts between subgroups Mean diff. (95% CI)</th>
<th>P Value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>102/104</td>
<td>8.5 (1.3)</td>
<td>6.7 (1.3)</td>
<td>1.8 (-1.8 to 5.4)</td>
<td>-5.1 (-13.3 to 3.1)</td>
<td>0.2241</td>
<td></td>
</tr>
<tr>
<td>BMI = 30</td>
<td>25/25</td>
<td>3.4 (2.6)</td>
<td>5.5 (2.6)</td>
<td>-2.0 (-4.2 to 5.1)</td>
<td>3.1 (-10.0 to 7.1)</td>
<td>0.3537</td>
<td></td>
</tr>
<tr>
<td>Swollen Study knee</td>
<td>35/37</td>
<td>9.1 (2.2)</td>
<td>5.0 (2.1)</td>
<td>4.1 (-1.9 to 10.1)</td>
<td>0.6 (-3.9 to 5.0)</td>
<td>0.5748</td>
<td></td>
</tr>
<tr>
<td>Bilateral TF-OA</td>
<td>10/11</td>
<td>7.4 (1.3)</td>
<td>5.9 (1.3)</td>
<td>1.5 (&lt;2.1 to 5.2)</td>
<td>4.9 (-6.2 to 15.6)</td>
<td>0.9155</td>
<td></td>
</tr>
<tr>
<td>Active as young adult</td>
<td>66/68</td>
<td>10.4 (1.6)</td>
<td>8.7 (1.5)</td>
<td>1.7 (-2.6 to 6.0)</td>
<td>2.1 (-3.8 to 8.0)</td>
<td>0.544</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>57/55</td>
<td>9.2 (1.7)</td>
<td>6.4 (1.8)</td>
<td>2.8 (-2.1 to 7.6)</td>
<td>0.6 (-4.7 to 5.9)</td>
<td>0.3941</td>
</tr>
<tr>
<td>Female</td>
<td>45/49</td>
<td>7.6 (1.9)</td>
<td>7.0 (1.9)</td>
<td>0.6 (6.4 to 5.7)</td>
<td>3.8 (13.8 to 7.6)</td>
<td>0.0639</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Above median</td>
<td>59/44</td>
<td>6.8 (1.7)</td>
<td>6.1 (2.0)</td>
<td>-0.6 (-6.4 to 5.7)</td>
<td>3.8 (-13.8 to 7.6)</td>
<td>0.0639</td>
</tr>
<tr>
<td>Below median</td>
<td>43/60</td>
<td>10.8 (2.0)</td>
<td>7.1 (1.7)</td>
<td>1.7 (-7.4 to 3.8)</td>
<td>6.1 (0.1 to 12.2)</td>
<td>0.0058</td>
<td></td>
</tr>
<tr>
<td>Preference*</td>
<td>33/46</td>
<td>6.3 (2.2)</td>
<td>8.1 (1.8)</td>
<td>1.8 (-7.4 to 3.8)</td>
<td>7.9 (-16.2 to 0.5)</td>
<td>0.0058</td>
<td></td>
</tr>
<tr>
<td>Analgesics</td>
<td>34/43</td>
<td>12.7 (2.2)</td>
<td>4.4 (1.9)</td>
<td>4.4 (2.6 to 14.1)</td>
<td>-1.9 (-6.4 to 2.5)</td>
<td>0.4108</td>
<td></td>
</tr>
<tr>
<td>Kellgren-Lawrence**</td>
<td>2 or 3</td>
<td>61/61</td>
<td>9.5 (1.6)</td>
<td>9.0 (1.6)</td>
<td>0.5 (-4.1 to 5.1)</td>
<td>3.5 (-20.0 to 9.1)</td>
<td>0.0069</td>
</tr>
<tr>
<td>Constant knee pain</td>
<td>41/43</td>
<td>7.0 (2.0)</td>
<td>3.4 (2.0)</td>
<td>3.6 (&lt;4.1 to 5.1)</td>
<td>3.5 (-20.0 to 9.1)</td>
<td>0.0069</td>
<td></td>
</tr>
<tr>
<td>Intermittent knee pain</td>
<td>47/35</td>
<td>12.6 (1.9)</td>
<td>5.0 (2.2)</td>
<td>7.6 (2.0 to 13.2)</td>
<td>-2.4 (-7.0 to 2.1)</td>
<td>0.0858</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2

Forest plot showing the results of the subgroup analyses based on the intention-to-treat population with missing outcome data at week 9 replaced with the baseline observation (non-responder imputation). The outcome is change from baseline in KOOS pain at week 9 (after 8 weeks of intervention). GLAD: The Good Life with osteoArthritis in Denmark exercise and education programme. OLP: Open-label placebo consisting of 4 intra-articular saline injections. K-L: Kellgren–Lawrence grading of radiographic disease severity. The full vertical line indicates the overall treatment effect, and the dashed line indicates zero effect. *24 GLAD and 26 OLP had no preference and are not included in the analyses, and 8 GLAD and 5 OLP had missing data; **For study knee.
Conclusion

In conclusion, these subgroup analyses may suggest that GLAD should be targeted to patients with knee OA who take analgesics for their knee pain or report constant knee pain on the ICOAP. The results represent the first step towards a much-needed stratified recommendation of exercise and education as management of knee OA and prompt for stratified tests of alternative treatments.

Contributions

E. Bandak, R. Christensen, H. Bliddal, L.E. Kristensen, and M. Henriksen conceived and designed the trial and the protocol that was reviewed and adjusted following important scientific and practical advice from K. Ellegaard, C. Bartholdy, D.J. Hunter, and R.D. Altman. E. Bandak was the trial manager. M. Henriksen, S.M. Nielsen and R. Christensen did statistical analyses. J. Guldberg-Møller and H. Bliddal had clinical responsibility. M. Henriksen drafted the first version of the manuscript. All authors read and critically revised the manuscript, and all authors approved the final manuscript and submission of the Article. E. Bandak and M. Henriksen had full access to all data in the trial and take responsibility for the data and the accuracy of the data analysis. M. Henriksen is the guarantor.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support for the submitted work as detailed above; no other relationships or activities that could appear to have influenced the submitted work.

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The funders had no role in the design and conduct of the study; collection, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2022.09.001.

Fig. 3

Proportional Venn diagram illustrating the overlap of participants in selected subgroups: Red area indicates participants with constant pain at baseline (n = 82), green area indicates participants who use analgesics at baseline (n = 77), blue area indicates participants with a treatment preference for GLAD (n = 64), and yellow areas indicate participants with no intermittent pain at baseline (n = 19). The area proportions are accurate, except for the yellow areas.
References


