Prevention and Rehabilitation

The effects of cognitive behavioural therapy delivered by physical therapists in knee osteoarthritis pain: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Recent evidence suggests that knee osteoarthritis (KOA) chronic pain can result in brain structural and organizational changes. Thus, patients’ pain level, emotional status, and perception of their condition might be negatively altered. An approach to reverse such adaptations to chronic pain is cognitive behavioural therapy (CBT). Combining CBT with exercise might enhance therapy outcomes.

Objectives: To identify the effect of combining exercise and CBT when delivered by a physical therapist in KOA pain.

Methods: A systematic search in PubMed, Cochrane, and Medline Complete (EBSCO) databases was conducted from their inception to March 2020, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Study risk of bias and quality were assessed through the Risk-of-bias 2 (ROB2) and PEDro scales.

Results: Six primary studies met eligibility criteria. All studies had a low risk of bias and were divided into two sub-groups, in-person interventions and distance interventions. Both groups of studies showed within group participant improvements. In regards of WOMAC pain subscale, our meta-analysis revealed an overall deduction of $-1.42$ (95% CI: $-1.76$, $-1.09$; $I^2 = 58\%$), $-1.62$ (95% CI: $-1.97$, $-1.27$; $I^2 = 0\%$) in centre-based intervention, and $-1.28$ (95% CI: $-1.75$, $-0.81$; $I^2 = 73\%$) in distance delivered intervention.

Conclusion: Combining exercise and CBT seems to be an effective method to reduce KOA pain, although it is based on a small number of studies. Further studies are needed to reveal any differences when each intervention is applied separately.

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1. Introduction

Knee osteoarthritis (KOA) is considered a major cause of disability in the older population (Vos et al., 2012). While this condition is characterized by a variety of symptoms, such as muscle weakness, reduced functionality, and joint instability (Fransen et al., 2015); pain is the major symptom that will lead an individual to seek medical care. Pain represents the brain’s response to noxious signals sent by the nociceptive system. When these signals reach above the individual’s threshold, the brain will respond with pain (Moseley and Butler 2013). When this alarm stays active for long periods (chronic pain), changes may be observed in the central nervous system (CNS) (Wand et al., 2011; Pelletier et al., 2015). These neuroplastic changes might alter the symptoms by altering the structure and organization of the brain (Pelletier et al., 2015). This maladaptation can be reversed with interventions such as cognitive or behavioural therapy (Pelletier et al., 2015). Cognitive behavioural therapy (CBT) is an intervention where patients’ thoughts, beliefs, and feelings regarding their pathology are addressed. Exercise, together with weight loss, are the most effective conservative approaches to treat KOA (Mills et al., 2018). Such interventions aim to reduce joint mechanical loading through weight reduction or increases in strength (Mills et al., 2018). Whilst the optimal treatment remains unknown, imaging improvements have provided novel insights into the contributions of the CNS to chronic pain in patients with other musculoskeletal disorders (Wand et al., 2011). These findings highlighted the need for...
clinicians to reconsider their approaches to musculoskeletal disorders (Pelletier et al., 2015; Mills et al., 2018). Multidimensional approaches that do not exclusively address KOA as a local pathology have therefore emerged, one of which being the combination of exercise and CBT.

Previously, the effects of CBT in KOA pain have been summarized in a systematic review independently of other interventions (Ismail et al., 2017). In addition, the available interventions that can improve the quality of life or psychological factors of patients with KOA were also evaluated in a previous review study (Briani et al., 2018). We believe that our systematic review will add to the body of evidence as we focused on the combination of both exercise and CBT in KOA pain. We are exploring how this pathology should be not exclusively addressed as a central (CBT) or local (exercise) pathology. In addition, our study is differentiated from the second review study (Briani et al., 2018), as we focus on alternate outcomes of interest and we further investigate the most suitable profession to apply such an intervention, being physical therapists. We consider that it is of high importance to investigate the effectiveness of cognitive interventions combined with exercise. Any positive results might enhance daily practice and thus reduce an individual’s symptoms. A better management of KOA population pain might further translate to a reduction of knee surgeries and possible benefits for health systems.

The aim of this systematic review is to reveal the effectiveness of combining exercise and CBT, delivered by physical therapists, in reducing KOA pain. Such an intervention, that consists of therapeutic exercise and psychological interventions shall ultimately be delivered either from a psychologist trained in therapeutic exercise, or from a physical therapist trained in CBT. Given that a KOA patient will most frequently visit a physical therapist when suffering from pain, we decided to limit our search to physical therapists. To the best of our knowledge, this is the first systematic review evaluating the combination of these two interventions, delivered by physical therapist in KOA pain.

2. Methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). The protocol of our study was not registered with the International Prospective Register of Systematic Reviews (PROSPERO).

2.1. Search strategy

Two researchers (AP & KG) independently searched PubMed, Cochrane, and Medline Complete (EBSCO) databases to identify randomized clinical trials that examine the effectiveness of exercise combined with CBT in patients with KOA. The literature searches were conducted from inception to March 2020, restricted to English language publications but no date restriction was applied. The search was performed using the Boolean operators AND, OR, parentheticals, and quotation marks and adjustments were made as needed to match each database’s particularities. The search strategy used the keywords: (knee osteoarthritis OR knee degradation OR knee pathology OR knee pain) AND (cognitive OR metronome OR coping OR behavioural OR somatisation OR pain catastrophizing OR mirror OR self-efficacy) AND (pain OR WOMAC OR VAS OR “Western Ontario AND McMaster Universities Osteoarthritis Index” OR “Numeric pain scale”). Additional information concerning the search strategy is presented in Supplementary Table 1. First, the title and abstract of each article identified through the search were examined, and then the full texts of potentially eligible articles were examined for evaluation. Discrepancies were resolved by mediation and discussion with a third author (DS). Reference list of relevant studies excluded or included was screened to identify additional studies.

2.2. Eligibility criteria and data extraction

Identification of the included studies was done following the PICOS characteristics (Participants, Intervention, Comparison, Outcomes, and Study type) criteria. Participants were only patients with KOA. As for the intervention, studies of CBT and exercise delivered by physical therapists were included; no co-interventions were allowed. For the comparison, studies that had a control/comparison group were eligible for inclusion. The chosen outcome was pain and the only study type eligible was randomized controlled clinical trial. Only studies written in English were considered with no restriction on the time of publication. We did not include review articles, dissertations or theses, published abstracts, book chapters, and points of view/expert opinions. In case of not-reported information, we contacted the corresponding author to request further information data.

Data extraction was performed independently by two authors (AP & KG) and any inconsistencies were resolved with discussion. From each eligible study, the following information was extracted: reference, subject details, intervention, session details, pain outcome measures and time of measures. Then this information was analyzed in order to categorize the included studies in subgroups for further analysis.

2.3. Quality assessment

For the assessment of the methodological quality of the included studies, the Cochrane risk of bias tool (RoB2) was used (Sterne et al., 2019). RoB2 is recommended for assessing the risk of bias in randomized trials. It consists of five domains, each focusing on a different aspect of the trial. Each domain has several signalling questions and an algorithm is then used to judge the methodological quality of the trial, based on answers to these. The categories for each question were classified as low, some concerns, or high risk of bias.

We used a second quality tool to compare the results and examine the studies again when disagreements occurred using the PEDro scale (Morton, 2009). PEDro scale is a 10 points scale where studies with a score over 6/10 are thought to be of low methodological bias. Each of the 10 questions can be answered with yes, no or unclear. We used the Best Evidence Synthesis (BES), modified by Tulder et al. (2003) to identify the level of evidence regarding the effectiveness of the techniques studied in our systematic review.

2.4. Data synthesis and statistical analysis

The main outcomes were synthesised qualitatively, based on descriptive statistics and/or the results of statistical analyses reported in the primary studies. All studies included presented pain levels as a continuous variable expressed as mean ± standard deviation (SD) or as mean (confidence interval).

Inverse-variance weighted approach was adopted for continuous data meta-analysis with a Standardized Mean Difference (SMD) and 95% Confidence Interval (CI), to estimate the size of the effect calculated by pooling the SMD of each individual study based on the mean, SD, and sample size. Two-tailed P value < 0.05 was considered statistically significant. We assessed heterogeneity among individual effect estimates and we reported the P value of the χ²-based Cochran Q test. The variation in estimates attributable to heterogeneity is quantified by the measure I² metric for inconsistency (Higgins and Thompson 2002). We expected statistical
heterogeneity, so we used the random effects model for the meta-analysis. To further explore sources of heterogeneity, we carried out subgroup analyses considering the intervention type (face-to-face or distance delivered). The presence of publication bias was examined by visual inspection of funnel plots and evaluated formally with Egger’s regression asymmetry test (Egger et al., 1997; Sterne et al., 2001). All statistical analyses were performed by STATA 14.0 software (STATA Corp, College Station, TX).

3. Results

3.1. Study selection

The databases search yielded 1836 relevant articles. After duplicates and non-RCTs were removed, 1251 articles remained. After a title and abstract screening, 35 studies were eligible for full-text screening. Twenty-one studies were further excluded because the intervention group was not supervised by a physiotherapist. Seven more studies were excluded because the subjects were not patients with only KOA, and 1 study was excluded because the intervention was not a combination of exercise and CBT. Thus, 6 studies were included in this systematic review. Further information concerning the study flow is presented in Fig. 1.

3.2. Study characteristics

A total of 800 patients were included in our systematic review. Participants in all studies included were on average over 45 years old and suffered from KOA. The total number of the patients included in the intervention and control groups was 373 and 427 respectively. The total number of males and females was 121 and 252 respectively in the intervention groups and 158 and 269 in the control groups. We divided the included study results into two categories. The first category included four studies that had a face-to-face setup (Kao et al., 2012; Hunt et al., 2013; Silva et al., 2015; Bennell et al., 2016) while the second one included two studies where a distance intervention was applied (Bennell et al., 2017; Hinman et al., 2019). In regards to pain intensity, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale was used in 5 of the included studies (Kao et al., 2012; Hunt et al., 2013; Bennell et al. 2016, 2017; Hinman et al., 2019). The Short-form 36 (SF-36) questionnaire was used by 2 trials (Kao et al., 2012; Silva et al., 2015), while the Numeric Rating Scale (NRS) was used in 3 (Hunt et al., 2013; Hinman et al., 2019; Bennell et al., 2016) studies. The Arthritis Self-Efficacy Scale (ASES) was used by 2 (Bennell et al., 2017; Hinman et al., 2019) studies and Lequesne index was used in 1 study (Silva et al., 2015). Main characteristics of the studies included are presented in Table 1.

3.3. Pain results

3.3.1. Face-to-face intervention group

Information concerning the pain results of face-to-face intervention is presented in Table 2. Kao et al. presented the total WOMAC score; thus, it was not possible to identify the results of WOMAC pain sub-scale separately. In the same study, SF-36 pain subscale scores were 70.5 ± 18.7, 70.0 ± 16.7, and 70.0 ± 16.7 at baseline, post-intervention, and on follow-up, respectively.
were no significant within-group changes group \((p < 0.241)\). In the second study (Hunt et al., 2013), the NRS score decreased from 4.2 ± 1.5 to 2.8 ± 1.6 and the WOMAC pain subscale decreased from 6.6 ± 1.0 to 1.7 ± 3.3. In the third study (Silva et al., 2015), the Lequesne pain subscale decreased from 4.93 ± 1.33 to 2.60 ± 1.55. The within-group change was statistically significant \((p < 0.05)\). The SF-36 pain subscale score decreased from 44.47 ± 11.78 to 57.60 ± 12.48 \((p < 0.05)\) in the same study. The last study included in this subgroup (Bennell et al., 2016) reported a Visual Analogue Scale (VAS) score decrease from 58.4 ± 12.8 to 26.4 ± 18.4 after intervention, 28.2 ± 21.6 at the first follow-up and 31.7 ± 22.6 at the second follow-up. The within-group pain decrease was statistically significant \((p < 0.01)\). Concerning WOMAC pain sub-scale, the authors reported a score of 9.0 ± 2.8 at baseline, 4.5 ± 2.9 after the intervention, 5.3 ± 3.3 at the first follow-up, and 5.2 ± 3.3 at the second follow-up.

### 3.3.2. Distance-delivered intervention group

The pain results of distance-delivered intervention group are presented in Table 3. In the first study of this group (Bennell et al., 2017) the WOMAC pain sub-scale score decreased from 9.0 ± 2.4 to 5.1 ± 2.7 post-intervention and 5.1 ± 2.9 at the first follow-up. The within-group difference from baseline to post-intervention was 3.9 \((3.1–4.7)\) with \(p < 0.05\) and 3.7 \((2.9–4.5)\) with \(p < 0.05\) from baseline to follow-up. The ASES pain sub-score increased from 6.1 ± 1.8 at baseline to 7.6 ± 2.0 and 7.5 ± 2.0 at post-intervention and follow-up, respectively (\(p < 0.05\)). In the second study (Hinman et al., 2019), the NRS pain score decreased from 6.0 ± 1.5 at

### Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Pain measure</th>
<th>Baseline [mean (SD)]</th>
<th>Post-intervention [mean (SD)]</th>
<th>Follow-up [mean (SD)]</th>
<th>Second follow-up [mean (SD)]</th>
<th>Baseline to Post-intervention [mean (SD)]</th>
<th>Baseline to follow-up [mean (SD)]</th>
<th>Baseline to second follow-up [mean (SD)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kao et al. (2012)</td>
<td>SF-36 pain</td>
<td>70.5 (18.7)</td>
<td>70.0 (16.7)</td>
<td>70.0 (16.7)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hunt et al. (2013)</td>
<td>WOMAC total score</td>
<td>38.5 (33.0)</td>
<td>41.7 (32.2)</td>
<td>41.2 (31.2)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Silva et al. (2015)</td>
<td>Lequesne Index pain</td>
<td>4.93 (1.33)</td>
<td>2.60 (1.55)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>(K.L. Bennell et al, 2016)</td>
<td>SF-36 pain</td>
<td>44.47 (11.78)</td>
<td>57.60 (12.48)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>WOMAC pain</td>
<td>58.4 (12.8)</td>
<td>26.4 (18.4)</td>
<td>28.2 (21.6)</td>
<td>31.7 (22.6)</td>
<td>3.14 (2.5)</td>
<td>&lt; 0.001</td>
<td>3.6 ± 2.9</td>
</tr>
<tr>
<td></td>
<td>WOMAC pain</td>
<td>9.0 (2.8)</td>
<td>4.5 (2.9)</td>
<td>5.3 (3.3)</td>
<td>5.2 (3.3)</td>
<td>4.3 (0.4)</td>
<td>&lt; 0.001</td>
<td>3.7 (0.4)</td>
</tr>
</tbody>
</table>

Abbreviations: WOMAC - Western Ontario and McMaster Universities Osteoarthritis Index; SF-36 – Short-form 36 questionnaire; NRS – Numeric Rating Scale; VAS – Visual Analogue Scale; CBT – Cognitively Based Programme; Exercise – Home-based exercise program prescription.
baseline to $3.5 \pm 2.1$ after intervention and to $3.9 \pm 2.4$ at follow-up. The WOMAC pain subscale score decreased from $8.6 \pm 2.7$ at baseline to $5.6 \pm 3.0$ post-intervention and $5.7 \pm 3.3$ at follow-up in the same study. Still in the same study, the ASES pain score increased from $5.9 \pm 1.6$ at baseline to $7.3 \pm 1.9$ after intervention and to $7.3 \pm 2.0$ at follow-up.

### 3.3.3. Meta-analysis results

For the purpose of the quantitative meta-analysis, data from four studies that used the WOMAC pain sub-scale for a total of 565 participant were combined. The pooled SMD for the 4 studies based on the random-effects model was $\bar{b} = -1.42$ (95% CI: $-1.75$, $-0.81$; $I^2 = 73\%$, P heterogeneity = 0.054, P < 0.0001) points in WOMAC pain subscale in comparison with control group. Distance delivered intervention subgroup resulted to a statistically important pain decrease with the overall WOMAC pain subscale pain difference was $-1.28$ (95% CI: $-1.75$, $-0.81$; $I^2 = 73\%$, P heterogeneity = 0.054, P < 0.0001) (Fig. 2).

### 3.3.4. Publication bias

The publication bias of the studies was determined by visual inspection of funnel plot for asymmetry or outliers and then evaluated formally with Egger’s regression asymmetry test. The shape of the funnel plot does not indicate obvious asymmetry (Fig. 3) and Egger’s test also provided non-significant results, suggesting no evidence of publication bias in the current meta-analysis.

### Table 3

<table>
<thead>
<tr>
<th>Study</th>
<th>Pain measure</th>
<th>Baseline [mean (SD)]</th>
<th>Post-intervention [mean (SD)]</th>
<th>Follow-up [mean (SD)]</th>
<th>Second follow-up [mean (SD)]</th>
<th>Baseline to Post-intervention [mean (SD)]</th>
<th>Baseline to follow-up [mean (SD)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al. (2017)</td>
<td>WOMAC pain</td>
<td>9.0 (2.4)</td>
<td>5.1 (2.7)</td>
<td>5.1 (2.9)</td>
<td>–</td>
<td>3.9 (3.1–4.7)</td>
<td>3.7 (2.9–4.5)</td>
</tr>
<tr>
<td></td>
<td>Self-efficacy</td>
<td>6.1 (1.8)</td>
<td>7.6 (2.0)</td>
<td>7.5 (2.0)</td>
<td>–</td>
<td>–1.5 (–2.0 to –1.0)</td>
<td>–1.3 (–1.8 to –0.8)</td>
</tr>
<tr>
<td>Hinman et al. (2019)</td>
<td>NRS pain</td>
<td>6.0 (1.5)</td>
<td>3.5 (2.1)</td>
<td>3.9 (2.4)</td>
<td>–</td>
<td>2.5 (2.0)</td>
<td>2.1 (2.2)</td>
</tr>
<tr>
<td></td>
<td>WOMAC pain</td>
<td>8.6 (2.7)</td>
<td>5.6 (3.0)</td>
<td>5.7 (3.3)</td>
<td>–</td>
<td>3.0 (2.5)</td>
<td>2.9 (2.9)</td>
</tr>
<tr>
<td></td>
<td>Self-efficacy</td>
<td>5.9 (1.6)</td>
<td>7.3 (1.9)</td>
<td>7.3 (2.0)</td>
<td>–</td>
<td>–1.4 (2.1)</td>
<td>–1.4 (2.0)</td>
</tr>
</tbody>
</table>

**Abbreviations:** WOMAC- Western Ontario and McMaster Universities Osteoarthritis Index; ASES- Arthritis Self-Efficacy Scale; NRS – Numeric Rating Scale.

- Expressed as mean (95% confidence interval).
- Expressed as $[mean (SD)]$.

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**Fig. 2.** Forest plot of standardized mean differences in WOMAC pain for the four included in the meta-analysis.
3.3.5. Methodological quality

As illustrated in Fig. 4, all the included studies had low risk of methodological bias according to the ROB2 tool. This result was further confirmed by the PEDro score. Two of the included studies were evaluated as 6/10 (Kao et al., 2012; Silva et al., 2015), two as 7/10 (Bennell et al., 2016, 2017) and two as 8/10 (Hunt et al., 2013; Hinman et al., 2019) (Table 4).

4. Discussion

In this systematic review we examined the effectiveness of CBT combined with exercise delivered by physical therapists in regards of KOA pain. Our findings suggest that the combination of CBT training and exercise can effectively reduce KOA pain. It is essential for a physical therapist, when managing an individual suffering from KOA, to interrupt his symptoms vicious cycle where pain will decrease activity and inactivity will lead to neural and muscular degeneration. According to our findings adding CBT to exercise might be altering any fault beliefs of a patient that might have been keeping him away from exercising or enhancing his pain.

4.1. Effectiveness of exercise and CBT combination on pain

The first study (Kao et al., 2012) did not report a significant change in pain levels in either pain outcome measure. It is impossible to know if there was a reduction in WOMAC pain subscale since the authors presented only the total score of that scale. In the remaining studies, centre based sub-group analyses (Hunt et al., 2013; Silva et al., 2015; Bennell et al., 2016) revealed improvements in all pain outcome measures. All the measurements (VAS, NRS, WOMAC, SF-36, and Lesquesne) showed improvements.

With regards to the distance-delivered intervention, both included studies (Bennell et al., 2017; Hinman et al., 2019) reported improvements in all of their pain measures. WOMAC and NRS scores decreased and the ASES increased. With 3 high-quality RCTs (Hunt et al., 2013; Silva et al., 2015; Bennell et al., 2016) in favour of this intervention and 1 not reporting effectiveness (Kao et al., 2012), it can be concluded that the combination of CBT and exercise delivered by physical therapists is supported with strong evidence of KOA pain reduction.

In order to identify the differences between combined treatment and with exercise only, studies should include groups where the subjects would only undergo exercise and compare their results to the suggested approach. Only one study (Bennell et al., 2016) had a group with an exercise-only approach. In that study, the vast majority of the measurements were equal and statistically nonsignificant. Thus, it is currently unclear whether CBT combined with exercise is superior to an exercise-only program.

To identify differences between the two interventions, only CBT groups should be included in the studies. Only one such study was done (Bennell et al., 2016) and it was seen that the combination of the two techniques was superior in the first follow-up according to the VAS score and at post-intervention and first follow-up according to the WOMAC pain subscale score. Thus, the results are conflicting and clear recommendations cannot be made. Our results
are in agreement with those of a previous systematic review (Ismail et al., 2017). Therefore, the authors reported no statistically significant decrease in WOMAC pain subscale of CBT independently, they report significant differences when CBT is combined with other interventions such as exercise.

4.2. Strengths and limitations

There are several strengths to our study. To the best of our knowledge, this is the first systematic review and meta-analysis that evaluates the available evidence from published RCTs on the effectiveness of the combination of these two interventions, delivered by physical therapist in KOA pain. Two reviewers independently and rigorously reviewed and extracted data to minimize the chance of error. In addition, individual studies were assessed for the risk of bias with validated assessment tools.

However, our systematic review presents some limitations. First, only articles written in English were considered, which could have resulted in missed studies. Further, the number of studies comparing the combination of the two interventions with each intervention independently was not sufficient to report any differences between these interventions. Our results cannot be generalized in all health professions since we included only physical therapist delivered intervention studies. Lastly, our search relied only in 3 databases thus it is unknown if any studies have been missed.

Clearly, further high-quality RCTs are needed in order to identify the differences between CBT/exercise with exercise or CBT alone. We opine that CBT interventions can be improved. We suggest that the differences between CBT/exercise with exercise or CBT alone. Furthermore, KOA is a condition that must be addressed not only as a local pathology. Current results are limited but show that by enhancing exercise programs with CBT, additional symptom improvements may take place. Further research is needed to identify the exact impact of such an approach.

5. Conclusion

While the combination of exercise and CBT is an effective approach for KOA pain when delivered by physical therapists, the results did not favour the use of this combination against each intervention alone. Furthermore, KOA is a condition that must be addressed not only as a local pathology. Current results are limited but show that by enhancing exercise programs with CBT, additional symptom improvements may take place. Further research is needed to identify the exact impact of such an approach.

5.1. Clinical relevance

- Current available evidence of CBT and exercise for KOA pain shows low risk of bias
- The overall findings show that the combination of both approaches has a positive effect in multiple pain outcome measures

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CRediT authorship contribution statement

Alexios Pitsillides: Conceptualization, Writing - review & editing, Formal analysis, Methodology. Dimitrios Stasinopoulos: Conceptualization, Writing - review & editing. Konstantinos Giannakou: Conceptualization, Writing - review & editing, Formal analysis, Methodology, Supervision. All authors read and approved the final manuscript.

Declaration of competing interest

There was no conflict of interest.

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The authors declare no conflicts of interest.

Appendix A. Supplementary data

 Supplementary data to this article can be found online at https://doi.org/10.1016/j.jbmt.2020.11.002.

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