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Reply to second letter to the editor about the article "The addition of blood flow restriction to resistance exercise in individuals with knee pain: a systematic review and meta-analysis"

We appreciate the comments by Korakakis et al.¹ on our article 'The addition of blood flow restriction to resistance exercise in individuals with knee pain: a systematic review and meta-analysis'.² We would like to take the opportunity to address several points raised in these comments which adds to the discussion that this review already generated.^{3,4}

First, we do not agree with the comment 'Although the authors reported that they conducted the review following recommendations in the Cochrane Handbook, there are some important departures, which have likely introduced biases and inconsistencies...' Our systematic review was performed according to the recommendations of the Cochrane Handbook and the PRISMA statement, which are the current guideline recommendations regarding systematic review design and methodologies.^{5,6} In addition, the results of the analysis of pooled data as performed by Korakakis et al.¹ and illustrated in their Figures (Figure 1A, $p = 0.94$, Figure 1B, $p = 0.65$) seem to be consistent with our conclusion of a lack of effect of blood flow restriction (BFR).

Second, despite the fact that the extracted data used different scales and scores, it was possible to perform a meta-analysis, according to the recommendations of the current Cochrane Handbook, using standardised mean differences to unify and adjust the values. Although this is not ideal and could be a source of heterogeneity, it allowed assessing the data in a more categorical manner with quantitative results.⁵

Additionally, it was suggested that we should have included the study by Tennent et al.⁷ Considering that its effect measures are expressed in medians and interquartile range, this is why it was not possible to include these data in the meta-analysis with our other data using RevMan 5.3 software.⁵ However, we tried to contact the corresponding author to request the data, but did not receive a response. In fact, the authors of the letter should change the estimator measure of standard error and variance in their forest plots (Figure 1A and 1B),¹ as it is not advisable in intervention studies reporting the effect with this estimator as it makes

the interpretation of the results difficult.^{8,9} Despite this, the magnitude of the effect remains small and not statistically significant.

Regarding the meta-analysis of knee function, unlike the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Knee Injury and Osteoarthritis Outcome Score (KOOS) functional scales, the Kujala score is a specific outcome measure for patellofemoral pain that includes symptoms, function, and quality of life in a single score.¹⁰ For this reason, the results of Giles et al.¹¹ were not considered in this quantitative analysis.

Regarding the inclusion of Korakakis et al.¹² this study was only considered for the descriptive and qualitative analysis and, therefore, did not influence the results of our meta-analysis.

Regarding the final statement '*The pooling of heterogeneous outcome measures, the discrepancies in eligible studies, and the overestimation of the pooled effect estimate suggest that these recommendations on the effectiveness of BFR should be interpreted with some caution*', while we understand the importance and caution about heterogeneity, the random effect model used in our meta-analysis attenuated this effect. Additionally, it is advisable to conduct a meta-analysis despite the presence of substantial heterogeneity as this is considered under the inconsistency domain when assessing the overall quality of evidence using the GRADE approach. These methodological aspects are described in the statistical methods' section of our review and follows the Cochrane Handbook, the PRISMA statement, and the GRADE recommendations.^{5,6,13,14}

Finally, we thank the authors of the letter for their concern for our study. We used a transparent method of assessing and reporting the evidence. All authors of systematic reviews with a meta-analysis must make methodological decisions, but these are not made with the aim of introducing bias or decreasing the evidence for effectiveness of treatment. None of the changes suggested by the authors of the letter substantially modify the results or the conclusions of our systematic review. An important aspect of our results is that it reinforces that more clinical studies and of better methodological quality are needed to demonstrate in which patients and at which dose BFR may be clinically effective.

Conflicts of interest

The authors declare no conflicts of interest.

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