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Efficacy of conservative treatments for hand osteoarthritis

An umbrella review of interventional studies

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Summary
Background Hand osteoarthritis (OA) is common, but the efficacy/safety of treatment interventions aimed to improve health outcomes in this population are not well understood. Therefore, the aim of this study was to map and grade the effect of interventions for health outcomes in hand OA.
Methods Umbrella review of systematic reviews with meta-analyses of randomized controlled trials (RCTs) using placebo/no intervention as control group. For outcomes with a *p*-value <0.05, the certainty of the evidence was evaluated using the grading of recommendations assessment, development and evaluation (GRADE) assessment.
Results From 189 abstracts, 9 meta-analyses (24 outcomes) were included, with 8 reporting significant summary results. The use of splints was associated with reduced pain at medium term in thumb carpometacarpal OA (standardized mean difference [SMD] = –0.70; 95% confidence intervals [95% CI]: –1.05 to –0.35; low certainty), reduced pain in long follow-up RCTs in symptomatic hand OA (SMD = –0.80; 95% CI: –1.16; –0.45; moderate certainty), and better function (SMD = 0.42; 95% CI: 0.08; 0.70; low certainty). The use of resistance training (SMD = –0.27; 95% CI: –0.47; –0.07) or physical exercise (SMD = –0.23; 95% CI: –0.42; –0.04) in improving hand pain and in improving finger joint stiffness (SMD = –0.36; 95%CI: –0.58; –0.15) was supported by a moderate certainty of evidence. The use of intra-articular hyaluronic acid in improving function (MD = 1.12; 95% CI: 0.61; 1.64; moderate certainty of evidence) was the only statistically significant pharmacological intervention.
Conclusion Only some non-pharmacological interventions are effective in improving health outcomes in hand OA and this evidence is supported by a moderate/low certainty, indicating the necessity of further interventional research.

Keywords Osteoarticular conditions · Physical activity · Splint · Randomized controlled trial · Meta-analysis

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Introduction

Hand osteoarthritis (OA) is a common condition in adults and older people. It is widely known that the presence of hand OA linearly increases with age, with women having higher rates than men, especially after the menopause [1]. In an American study comparing

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the incidence of different forms of OA in a population living around Boston, using only radiological information the authors found that the highest incidence was found for knee OA (240/100,000 person-years), with intermediate rates for hand OA (100/100,000 person-years) and lowest observed rates for hip OA (88/100,000 person-years) [2]. These figures were overall confirmed in other surveys, such as in Europe [3].

Hand OA seems to be associated with several negative outcomes including a high rate of disability [4] and poor quality of life [5], whilst the association between hand OA and cardiovascular disease [6] or mortality [7] is less clear; however, hand OA is characterized by a high level of pain, stiffness and finally limited function making this condition very relevant from a clinical point of view [8]. Despite the clinical importance of hand OA, only a few treatments are approved for treating the symptoms (pain, stiffness, poor function) associated with this condition [9]. In 2007, the European League Against Rheumatism (EULAR) proposed some nonpharmacological and pharmacological interventions based on expert opinions [10], whilst in 2018 other authors updated these recommendations, even if the evidence was mainly based on the credibility of single randomized controlled trials (RCTs) [11].

Given this background, we aimed to capture the breadth of outcomes associated with interventions in people affected by hand OA and systematically assessed the quality, strength and credibility of these associations. We used the umbrella review methodology to combine evidence from a wide range of outcomes and populations including only RCTs.

Material and methods

Data sources and searches

We conducted an umbrella review [12], searching MEDLINE, Scopus, Embase databases until 31 December 2019 with: "(Meta-Analysis[ptyp] OR meta-analy*[tiab] OR meta-analy*[tiab] OR Systematic review [ptyp] OR "systematic review" [tiab]) AND (hand osteoarthritis [tiab])". In addition, we hand-searched the reference lists of eligible and other relevant articles.

Study selection

For the aims of this work, we included formal systematic reviews with meta-analyses of interventional studies, which investigated the effect of any kind of intervention (except surgical ones) for the treatment of hand OA. The authors JD and NV performed title and abstract screening, with another independent author (LS) available if needed. Full texts of all potentially eligible articles were then retrieved by the same two authors and any disagreement was resolved with another independent author (LS).

We included meta-analyses that investigated people affected by hand OA and including RCTs, with at least one group taking placebo or no active intervention, exploring the association of any kind of intervention with any health-related outcome. The type of intervention was consequently categorized as pharmacological and nonpharmacological depending on the nature. Nutritional supplementations were included among the pharmacological interventions. Meta-analyses were included only if they reported study-specific information (i.e. effect size, 95% confidence intervals [95% CI], sample size) or such information could be inferred from the presented data.

Data extraction

Two independent investigators (JD, NV), extracted key information for each meta-analysis: first author name; publication year; type of intervention; comparison group; hand OA definition; outcome of interest; follow-up (in months); number of people randomized to active intervention and those randomized to placebo/no intervention. We also extracted the study-specific estimated relative risk for health outcome (mean difference [MD]; standardized mean difference [SMD]) and 95% CI. We finally extracted the data for the assessment of multiple systematic reviews (AMSTAR)-2 tool [13].

When more than one meta-analysis on the same research question was identified, the one with the largest number of participants was selected.

Quality assessment

We assessed the methodological quality of the included meta-analyses using AMSTAR-2 [13, 14] that ranks the quality of a meta-analysis from critically low to high according to 16 predefined items.

Data synthesis and analysis

For each meta-analysis, we recalculated the summary effect size and its 95% CI by using the random effects DerSimonian and Laird [15]. We also estimated the prediction interval (PI) and its 95% CI, which further accounts for between-study effects and estimates the certainty of the association if a new study addresses that same association [16, 17]. Between-study inconsistency was estimated with the I^2 metric, with values ≥50% indicative of high heterogeneity [18].

We then calculated the evidence of small study effects (i.e. whether small studies inflated effect sizes). We used the regression asymmetry test [19], using a *p*-value <0.10 with more conservative effects in larger studies as indicative of small study effects [20].

All the analyses were conducted with STATA 13.0 (Stata Corp LP, College station, TX, USA).

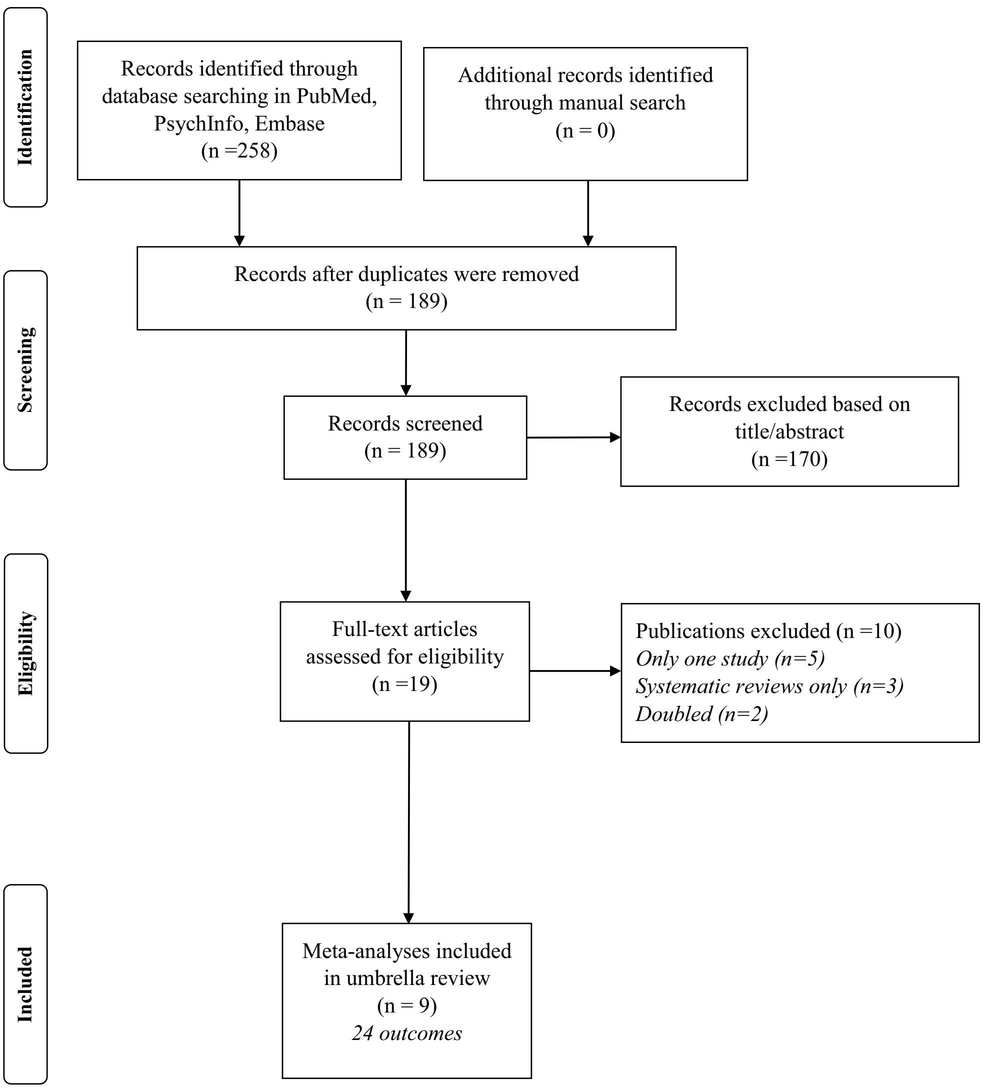

Fig. 1 PRISMA flow-chart for the selection of the studies included

Grading the evidence

Evidence from meta-analyses of RCTs was assessed in terms of the significance of the summary effect, using a *p*-value <0.05 as the threshold for statistical significance, as recently proposed [21, 22]. For significant outcomes, we evaluated the evidence using the grading of recommendations, assessment, development and evaluation (GRADE) assessment [23]. We also considered 95% PIs (excluding the null or not), small study effects ($p > 0.10$), and if the largest study was statistically significant or not, as possible indicators of bias in the available evidence.

Results

As shown in Fig. 1, we identified 189 unique works in 3 major databases, with 9 meta-analyses (corresponding to 24 different outcomes) finally included in our umbrella review [24–32].

Meta-analyses of RCTs (vs. placebo/no treatment)

As reported in Supplementary Table 1, the median number of RCT meta-analyses for each outcome was only 2 (range 2–6), the median number of participants was 164 (130–702). Overall, 18/24 of the interventions were ranked as nonpharmacological, and the most frequent intervention were physical exercise interventions ($n = 6$ outcomes) and the use of splints ($n = 10$). Regarding the site of hand OA affected, 8 outcomes included all types of hand OA and subtypes, 6 only symptomatic forms, the other 10 thumb-carpometacarpal, only thumb or trapeziometacarpal forms. Finally, 14 outcomes included evaluation of pain, followed by 8 investigating function as outcome, 1 handgrip strength and another 1 stiffness.

Overall, one third of the outcomes included (8/24) reported nominally significant summary results ($p < 0.05$). Table 1 shows the strength of the association between proposed interventions and selected outcomes in people affected by hand OA, using the

Table 1 GRADE evidence of randomized controlled trials using nonpharmacological and pharmacological interventions for hand osteoarthritis

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Type of intervention (vs. control group)	Anticipated absolute effects	
							With no intervention	With intervention		Risk with no intervention	Risk difference with intervention
Pain (medium follow-up, 3–12 months) in thumb carpometacarpal osteoarthritis											
137 (2 RCTs)	Serious[a]	Not serious	Not serious	Serious[b]	None	◯◯ LOW	65	72	Splints (vs. no splints)	–	SMD –0.70 (–1.05 to –0.35)
Function (medium follow-up, 3–12 months) in thumb carpometacarpal osteoarthritis											
135 (2 RCTs)	Serious[a]	Not serious	Not serious	Serious[b]	None	◯◯ LOW	66	69	Splints (vs. no splints)	–	SMD 0.42 (0.08–0.77)
Pain (long follow-up) in symptomatic hand osteoarthritis											
152 (2 RCTs)	Not serious	Not serious	Not serious[b]	Serious[b]	None	◯ MODERATE	75	77	Splints (vs. no splints)	–	SMD –0.80 (–1.16 to –0.45)
Hand pain											
381 (5 RCTs)	Serious[c]	Not serious	Not serious	Not serious	None	◯ MODERATE	193	188	Resistance training (vs. no resistance training)	–	SMD –0.27 (–0.47 to –0.07)
Finger joint stiffness											
368 (4 RCTs)	Serious[c]	Not serious	Not serious	Not serious	None	◯ MODERATE	188	180	Physical exercise (vs. no exercise)	–	SMD –0.36 (–0.58 to –0.15)
Pain in hand osteoarthritis											
492 (5 RCTs)	Serious[c]	Not serious	Not serious	Not serious	None	◯ MODERATE	246	246	Physical exercise (vs. no exercise)	–	SMD –0.23 (–0.42 to –0.04)
Pain in trapeziometacarpal osteoarthritis											
185 (4 RCTs)	Not serious	Very serious[d]	Not serious	Serious[b]	Publication bias strongly suspected[e]	◯◯◯ VERY LOW	91	94	Physical and occupational therapy (multimodal) (vs. no intervention)	–	MD –3.17 (–5.63 to –0.71)
Function in thumb osteoarthritis											
148 (2 RCTs)	Not serious	Not serious	Not serious[b]	Serious[b]	None	◯ MODERATE	74	74	IAHA (vs. placebo)	–	MD 1.12 (0.61–1.64)

CI confidence interval, *SMD* Standardized mean difference, *MD* mean difference
[a]Presence of detection and performance bias in both RCTs
[b]Small sample size (<100 participants in each arm)
[c]risk of detection bias on self-reported outcomes (lack of blinding of participants)
[d]$I^2 \geq 75\%$
[e]Eggers' test (*p*-value) <0.05

GRADE. Among seven nonpharmacological interventions, the use of splints was associated with reduced pain sensation at medium term in thumb carpometacarpal OA (SMD = –0.70; 95% CI: –1.05 to –0.35; low certainty of evidence), reduced pain in long follow-up RCTs in symptomatic forms of hand OA (SMD = –0.80; 95% CI: –1.16; –0.45; moderate certainty of evidence) and a better function (SMD = 0.42; 95% CI: 0.08; 0.70; low certainty of evidence), in two RCTs for each outcome. The certainty of evidence was mainly given by the small sample sizes included in these RCTs.

A moderate certainty of evidence supported the use of resistance training (5 RCTs, SMD = –0.27; 95% CI: –0.47; –0.07) or physical exercise (5 RCTs, SMD = –0.23; 95% CI: –0.42; –0.04) in improving hand pain and the use of physical exercise in improving finger joint stiffness (4 RCTs, SMD = –0.36; 95% CI: –0.58; –0.15) (Table 1). Conversely, the use of a multimodal intervention was associated with an improvement in pain in trapeziometacarpal OA supported by a very low certainty of evidence.

The only pharmacological intervention associated with a significant outcome was the use of intra-articular hyaluronic acid in improving function in people affected by thumb OA (MD = 1.12; 95% CI: 0.61; 1.64; moderate certainty of evidence).

Supplementary Table 1 shows other analyses commonly used in the umbrella review methodology. Three outcomes reported a small study effect, in six outcomes the largest study, in terms of participants, was statistically significant, and only one outcome reported the PIs not including the null value.

As reported in Supplementary Table 2, four meta-analyses were rated high according to the AMSTAR-2 criteria, whilst three other meta-analyses were rated as low and two as critically low.

Discussion

With this work, we provide a comprehensive overview of the potential pharmacological and nonpharmacological interventions in people affected by hand OA, incorporating evidence from nine meta-analyses. In this respect, we assessed the evidence of RCTs using the GRADE assessment, in order to increase the transparency of this evidence. Overall, we found that among 24 different interventions investigated, only 8 were supported by a statistical significance and of these, 5 reached a moderate certainty of the evidence. The AMSTAR-2 indicated that works included were accurate in describing risk of bias in studies included in meta-analysis. Moreover, the meta-analysis included often presented and followed pre-established protocols and reporting models, such as PRISMA.

Our umbrella review showed that the large majority of the interventions for hand OA involved nonpharmacological interventions, in particular splints. Using the most common categorization for SMD (i.e. small, moderate, or large effect, if the SMD was 0.2–0.5, 0.5–0.7, and ≥0.7, respectively) [33], we observed that splints are able to significantly reduce pain in thumb carpometacarpal and in symptomatic OA with a large effect, even if this evidence is supported only by a low/moderate certainty of evidence using the GRADE. From a clinical point of view, it seems that splints might provide a material support of inflamed joints, finally reducing inflammation with a consequent reduction in pain [24, 34, 35]. A similar effect was suggested for improving function: in our umbrella review, the improvement in function was moderate according to the SMD, but again suffered on the presence of bias and of limited sample size. Among nonpharmacological interventions the other that we found to be significant was physical exercise [36]. In this case, physical exercise, in particular resistance training, decreased pain with a small effect and, again, the effect of potential biases and imprecision as shown in the GRADE assessment are unfortunately of importance. Further specific research is needed regarding the importance of physical exercise in improving hand OA outcomes.

In our umbrella review, the only pharmacological intervention statistically superior to placebo was intra-articular hyaluronic acid in improving function in people specifically affected by thumb OA, in agreement with a robust review regarding this topic [37]. This is somewhat surprising since several medications are commonly used for improving pain and function in hand OA, including topical and oral nonsteroidal anti-inflammatory drugs, paracetamol, glucocorticoids, intra-articular medications and many others [11, 38–41]. In this respect, the most commonly used guidelines for hand OA [10, 11] recognize that very limited research is available on this specific condition regarding medications that are commonly used for types of OA, such as knee OA [42]. Our work further supports the need for high-quality RCTs for hand OA, also due to its clinical and epidemiological importance [8].

The findings of our work should be interpreted within its limitations. First, we used evidence assessment criteria, which were based on already established tools for evaluating the current evidence that are biased for their nature [43]. Moreover, meta-analyses included studies with relevant differences in design, population and other basic characteristics that can increase the risk of high heterogeneity. In order to overcome this problem, we used an $I^2 < 50\%$ as one of the domains of the GRADE. Second, another common limitation of an umbrella review approach is the use of existing meta-analyses that are related to choices made about what estimates to select from each primary study and how to represent them in the meta-analysis. Third, in this umbrella review half of the outcomes included only two RCTs and most of the RCTs included small sample sizes strongly limiting our results. It is noteworthy, for example, that only one outcome (i.e. the use of physical exercise in reducing pain) had 95% PIs excluding the null value.

In conclusion, our umbrella review including 9 meta-analyses and 24 different outcomes in people affected by hand OA, found that only a few nonpharmacological interventions are potentially effective in improving health outcomes and this evidence is supported by a moderate/low certainty of evidence according to the GRADE. Our work further encourages specific research of high-quality RCTs in order to increase the availability of interventions for improving outcomes in people affected by hand OA.

Compliance with ethical guidelines

Conflict of interest N. Veronese, L. Smith, F. Bolzetta, A. Cester, J. Demurtas, and L. Punzi declare that they have no competing interests.

Ethical standards For this article no studies with human participants or animals were performed by any of the authors. All studies performed were in accordance with the ethical standards indicated in each case.

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