TITLE: Overall Effects and Moderators of Rehabilitation in Patients With Wrist Fracture: A Systematic Review

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Abstract

Objective. Wrist fractures constitute the most frequently occurring upper limb fracture. Many patients report persistent pain and functional limitations up to 18 months following wrist fracture. Identifying which patients are likely to gain the greatest benefit from rehabilitative treatment is an important research priority. This systematic review aimed to summarize effectiveness of rehabilitation after wrist fracture for pain and functional outcomes and identify potential effect moderators of rehabilitation.

Methods. A comprehensive search of 7 databases (including MEDLINE, EMBASE, and the Physiotherapy Evidence Database [PEDro]) was performed for randomized controlled trials involving adults >50 years of age who sustained wrist fracture and had received 1 or more conservative treatments (eg, exercise/manual therapy, lifestyle, diet, or other advice). Study selection, data extraction, and risk-of-bias assessment were conducted independently by 2 reviewers. Results of included trials were summarized in a narrative synthesis.

Results: A total of 3225 titles were screened, and 21 studies satisfying all eligibility criteria were reviewed. Over half of included studies (n = 12) comprised physical therapist and/or occupational therapist interventions. Rehabilitative exercise/manual therapy was generally found to improve function and reduce pain up to 1 year after wrist fracture. However, effects were small, and home exercises were found to be comparable to physical therapist–led exercise therapy. Evidence for the effects of other nonexercised therapy (including electrotherapy, whirlpool) was equivocal and limited to the short term (< 3 months). Only 2 studies explored potential moderators, and they did not show evidence of moderation by age, sex, or patient attitude of the effects of rehabilitation.

Conclusion: Effectiveness of current rehabilitation protocols after wrist fracture is limited, and evidence for effect moderators is lacking. Currently available trials are not large enough to produce data on subgroup effects with sufficient precision. To aid clinical practice and optimize effects of rehabilitation after wrist fracture, potential moderators need to be investigated in large trials or meta-analyses using individual participant data.

Impact. Many patients report persistent pain and functional limitations up to 18 months following wrist fracture. Effectiveness of current rehabilitation protocols after wrist fracture is limited and may be due to insufficient targeting of specific rehabilitation to patients who are likely to benefit most. However, evidence for effect moderators is lacking within currently available literature. To aid clinical practice and optimize effects of rehabilitation, investigating potential moderators of rehabilitation in patients with wrist fracture via large trials or meta-analysis of individual participant data is research and policy imperative.

[H1]Background

Fractures of the wrist account for 25% of all fractures in the United Kingdom[1,2] and result in a 5-fold increase in healthcare utilization and associated expenditures in the year post fracture.[3] In terms of disease burden, 63% of people with upper limb fracture report ongoing pain 6 months post fracture, and up to 15% develop complications such as persistent neuropathies, long-term impairment, and complex regional pain syndrome.[4-6]

In adults aged over 50 years old, wrist fractures are likely to represent a fragility fracture, defined as fractures which occur following an episode of low trauma.[7,8] Such fractures are often the first indicator of poor bone health and are associated with debilitating consequences with respect to activities of daily living such as work, driving, mobility, and self-care, leading to: loss of independence; re-fracture at other sites; reduced quality of life; increased health and social care consumption; and up to a 14% increase in mortality rates 7 years post-fracture.[5,6,9-13]

Fragility wrist fractures may also be an early signal in the life course of a middle to older aged adult, indicating the potential for a cascade of further adverse events (eg, falls, other fragility fractures, frailty, multi-morbidity, and polypharmacy). As such, fragility wrist fractures are a key target for early rehabilitation, whilst the potential for rehabilitation is at its maximum.

Treatment of wrist fractures include surgical and non-surgical (conservative) approaches.[14] Clinical decision making regarding the balance of potential harms and benefits of different treatment options usually varies depending on the patient.[14] Regardless of the treatment chosen, rehabilitation is a core component of a post-fracture care plan and may involve any or all of the following: occupational therapy; education and advice; diet and lifestyle interventions; pharmacy review; falls prevention; exercise therapy; and a variety of splinting devices and electro/magnetic therapies.[15]

However, within currently available literature, the observed effect sizes for reducing pain and improving function following wrist fracture are mostly small and highly imprecise.[3,14,16] Findings of less-than-optimal effectiveness of rehabilitation post wrist fracture may result from insufficient targeting of rehabilitation to patients with wrist fractures who are likely to benefit most. Concerns about the effectiveness and generalizability of existing treatments for post wrist fracture rehabilitation exist because of varying rehabilitation protocols, and different patient profiles. The degree to which rehabilitative treatments match the needs of patients with wrist fracture is germane to clinical decision making and to optimize efficacy of care. Identification of key characteristics of optimal rehabilitative treatment protocols (including therapy utilization,

timing, duration, and technique), and understanding of moderating factors are imperative for the development of effective patient-centered wrist fracture rehabilitation protocols. Moderators are factors that affect the direction and/or strength of treatment effect, and may include patient characteristics, such as age, sex, lifestyle, characteristics of the fracture, or comorbidity.[13]

This systematic review therefore aims to summarize evidence for:

(a) The overall effects of rehabilitative treatments for patients with wrist fracture.

(b) Potential moderators (predictors) of the effects of treatments for patients with wrist fracture.

[H1]Methods

[H2]Protocol and Protocol Registration

This systematic review was written using the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidance statement.[17] The review also aligns with the Synthesis without meta-analysis (SWiM) in systematic reviews reporting guideline.[18] A full protocol was established for this study and was registered a priori on the international prospective register of systematic reviews (Prospero ID: CRD4201810776).

[H2]Information Sources and Search Strategy

A comprehensive search strategy was developed by an information specialist as part of the review team which included clinicians, physical therapists, and academics with subject knowledge of wrist fracture and osteoporosis. A search of the following electronic databases was conducted from their inception until April 2020: Medline, EMBASE, CINAHL, AMED, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science (see Fig. 1 for full search strategy). Database searches were supplemented by hand searching bibliographies of eligible articles and other relevant literature in the field to identify additional studies and grey literature.

[H2]Study Selection and Eligibility

The review process was managed using the Covidence software package (https://www.covidence.org). Using pre-defined eligibility criteria, 2 independent reviewers screened the titles and abstracts of retrieved citations. Conflicts were resolved with discussion or by the independent opinion of a third reviewer. Studies progressing to full-text stage were similarly screened. The following criteria were used to assess eligibility of each trial to be included in the review:

[H3]Participants:

Adults (50 years of age and over) with a history of wrist fracture. As many trials included participants from a wider age range, we considered trials that reported a mean age -1 SD (standard deviation) totaling >45, to ensure the majority of participants in eligible trials were 50 years or older.

[H3] Interventions/Exposures:

Any conservative (non-surgical) treatment including any of the following: diet and exercise, falls prevention, occupational therapy, exercise therapy, acupuncture, and electromagnetic therapies. Primary studies focusing on pharmaceutical and/or nutraceutical treatments only were excluded from this review.

[H3] Comparisons or Control Arms:

Control group including placebo, no intervention, or comparison with other conservative interventions.

[H3] Outcomes of Interest:

a) Primary outcome of interest was pain and functional disability following wrist fracture.

b) Secondary outcomes included post-treatment complications, quality of life, healthcare utilization, and work absence.

[H3] Study Design:

Only randomized control trials (RCTs) were included. (RCTs were required for moderation analysis, therefore no other study types considered).

[H2]Data Extraction

Eligible full texts were subjected to data extraction using a pilot tested data extraction form, customized for this review. The aim(s), rationale, design, study setting, inclusion and exclusion criteria for each of the eligible studies were documented. Study-level data were also collected on participant characteristics including details of treatments received (type, duration, intensity, and frequency of sessions); concurrent intervention (where reported); treatment uptake; outcome measures; treatment outcomes; follow-up time points; potential predictors of treatment effect; and complications. Data regarding the use of subgroup or moderation analysis including estimates of subgroup effects or associations between potential predictors and treatment effects were also sought from included studies. Full data extraction was conducted for all included studies by 1 reviewer and was checked by an independent second reviewer to ensure validity and consistency of extracted data.

[H2]Risk of Bias Assessment

Two independent reviewers assessed eligible full texts based on the Cochrane Risk of Bias tool.[19] Reviewers were blinded to the responses from the other reviewer until both reviewers had completed their reviews. Disagreements were resolved with discussion.

[H2]Methodological Quality of Moderation Analysis

Assessment of the quality of moderation analysis was based on existing quality criteria, outlined by Pincus et al (2011), which provide an estimation of the level of moderation evidence.[20] The 5 criteria considered when making a judgement on the overall level of evidence for moderation include an a priori hypothesis, presence of a theory or evidence-based selection of moderators to be tested, measurement of moderators prior to randomization, quality of measurement of baseline factors, and an explicit test of the effect of interaction between moderator and treatment on outcome. Each criterion is scored as either met or not met, resulting in a total score ranging from 0 to 5. A maximum score of 5 out of 5 allows findings to be regarded as confirmatory evidence, while the presence of 3 criteria allow findings to be regarded as exploratory evidence.[19]

[H2]Data Analysis and Synthesis

Statistical pooling of data (via random effects meta-analysis) was not possible as planned because of the substantial differences in patient population, settings, interventions, and outcomes used. This systematic review therefore followed a narrative approach.[19,20] Synthesis involved an initial description of the characteristics of the included studies and their risk of bias. Included studies were subsequently grouped into broad categories by intervention type (eg, exercise/manual therapy as part of physical therapy or occupational therapy; other non-exercise therapy including acupuncture, electrotherapy, aids/orthotics), and results reported in relation to review outcomes (ie, pain and functional disability). A summary of evidence from studies which included analysis of, or suggested moderators of treatment outcomes, was then undertaken. For this, studies were categorized into 2 groups: (i) studies with further analysis of between-arm treatment effect for patient subgroups (or formal moderation analysis) and (ii) studies that suggested potential moderators of treatment effect without formal analyses.[21]

[H1]Role of The Funding Source

The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR, or the Department of Health and Social Care. The funders played no role in the design, conduct, or reporting of this study.

[H1]Results

In the subsequent paragraphs, a description of all included studies, including risk of bias and treatment effects (grouped by intervention type), is given first. This is followed by a description of the moderators highlighted in the body of evidence and an evaluation of the level of evidence for moderators of treatment effect.

[H2]Characteristics of Included Studies

Details of the study identification and selection process is illustrated in Figure 2. After removing duplicates (n = 3216), our search strategy yielded 3550 unique titles which were screened. Of these, 3225 were found to be irrelevant during title and abstract review. A total of 325 studies qualified for full-text review, and 21 of these fully met pre-specified eligibility criteria and were included in the final review. Reasons for exclusion of full-text articles included pediatric patient population, surgical interventions, irrelevant outcomes (eg, radiological) and non-randomized study designs.

Included studies were published over a period of 34 years between 1986 and 2020.[22-24] Studies were conducted across Europe[9,25-32], North America[22,33,34], South America[35], Asia[36,37,38], and Australia.[23,39-41] All of the studies were conducted in the primary care/community sector (though this was not part of our inclusion criteria). A total of 1065 participants with a mean age of 57.8 years and ranging from 49.9 years of age (SD 10.15) to 75.85 years of age (SD 7.65) were included in this review.[27,39] Sample sizes of included studies ranged from 18 to 119 participants.[26,39] On average, study samples consisted of a greater proportion of females compared to males: mean proportion of females was 75.9%; this ranged from 34% to 100%[26,28]. One study did not give data on sex.[23] In terms of fracture types and severity, most studies did not specify or report fracture classifications but where reported, fracture severity was variable. Included studies recruited patients with distal radial fractures (n = 16), 2 studies recruited people with Colle fractures while the rest included mixed population involving different types of fractures at the wrist. The characteristics of included studies are summarized in Supplementary Table 1.

[H2]Risk of Bias

Of the 21 studies included, only 2 were assessed as having low risk of bias in all domains of risk assessment, which were also the only 2 studies assessed as having low risk of bias in relation to blinding of participants and personnel.[23,34] This domain also had the highest number of studies (n = 13) assessed as having unclear risk of bias due to insufficient information to adequately assess risk.[22,25–27,29,31,32,35,37–41] Though 14 studies had a low risk of selective reporting of outcomes, this domain also accounted for the highest number of studies (n = 6) having a high risk of bias. Reasons contributing to other sources of bias in included studies were deviation from protocol,[38] not presenting data on baseline characteristics[23], not clearly stating how patients were recruited[28] and selective presentation of significant outcomes.[25,28,31,33,37,39] Summary of risk of bias for each included study is presented in Figure 3.

[H2]Outcome Measures

Pain and function were the primary outcomes for this systematic review, although included studies also investigated secondary outcomes of interest: post-treatment complications (n = 6), quality of life (n = 3), healthcare utilization (n = 0), and work absence (n = 2). The Patient Related Wrist Evaluation Score (PRWE) was the most commonly used outcome measure to assess pain, function, and difficulty performing everyday activities.[24,26,27,30,33–36,40,41] Other measures used to assess pain were the Visual Analogue Scale (VAS),[23,24,26,30,35] and the present pain intensity score (PPI).[22] In terms of function, the Disabilities of the Arm, Shoulder

and Hand questionnaire (DASH) or QuickDASH were often used in combination, or as an alternative, to PRWE for investigating the level of functional disability in performing everyday activities.[9,23,24,26,27,35] Other outcome measures used to assess function were the Werley functional score[25] encompassing pain, disability, ROM (range-of-motion), and radiography,[23] and the Michigan Hand questionnaire (MHQ), which investigates pain, function, satisfaction and activities of daily living.[27]

[H2]Effectiveness of Conservative Treatments Following Wrist Fracture

Supplementary Table 2 presents a summary of results for studies reporting pain and function outcomes of conservative treatments post wrist fracture.

[H3] 1. Exercise/Manual Therapy as Part of Physical Therapy or Occupational Therapy

[H4]Interventions

Sixteen studies[9,23–26,28–31,33-35,38–41] investigated exercise as part of physical therapist/occupational therapist-led interventions. Occupational therapy exercises included hand strengthening and function focused programs[23,25]. In addition to localized rehabilitation of the hand affected by wrist fracture, physical therapist-led exercise intervention studies also focused on the impact of the onset of rehabilitation (early versus late mobilization[24,26,30,38]) and mode of delivery on treatment effectiveness. Delivery modes were mainly home-based exercise with or without physical therapist-led sessions versus physical therapist-led exercise rehabilitation.[28,31,33,35,39,40] Other comparisons to physical therapist-led exercises included the use of an advice brochure[28].

The duration of intervention ranged from 2 weeks,[29] to 52 weeks.[24] Two studies did not specify the duration of treatment for either intervention or control arms.[22,31] Frequency of therapy varied between 3 times a day,[40] and once a week.[23] Though over 50% of patients in treatment arms completed some form of home-based exercise protocol (constituting up to 70% of their treatment schedule), there was no significant difference in adherence to exercise/rehabilitation protocols between control and intervention arms of studies that reported adherence.[33,38]

[H4]Effects on pain

Nine out of 16 studies assessing the effects of exercise as part of physical therapist/occupational therapist-led interventions reported on pain outcomes.[23,24,26,28,30,31,35,40,41] Exercise was associated with reduction in pain but reported effects/differences between treatment arms were mostly limited to the short term (<6 months) and were not statistically significant.[23,24,30,31,35,40,41] Only 2 studies, found exercise to reduce pain symptoms for up to 1 year after wrist fractures.[26,28] There was discrepancy amongst the studies regarding any perceived advantage of physical therapist-led exercises over home-based exercise on pain outcomes.[26,28,30,31,40,41] Most studies reported no significant difference between either mode of delivery in the short- or long-term.[28,31,40, 41] In summary, the effect of exercise on pain after wrist fracture is limited and, home exercises were found to be comparable to physical therapist-led exercise therapy, especially when used in combination with less frequent conventional 1-to-1 physical therapist-led sessions.[26,28,30,31,40,41]

[H4]Effects on function

All 16 studies reported on the effects of exercise on functional outcome after wrist fracture. Only in 5 studies was exercise/manual therapy utilized as part of physical therapy/occupational therapy rehabilitation programs reported to lead to significant improvements in hand function compared to control.[9,23,24,30,35] For up to 1 year after commencing exercise rehabilitation for wrist fracture, most studies reported no clinically significant differences between treatment arms. Studies with longer follow-up reported worsened or no significant improvement compared to control and/or other active interventions at any given time point up to 2 years.[26,28] As with pain outcomes, there were equivocal findings with regards to the beneficial effects or added advantage of physical therapist/occupational therapist-led exercises over home-based exercise for functional outcomes.[22,27,32,36,37,26,28,30,31,40,41]

[H3] 2. Non-Exercise Interventions Including Acupuncture, Electromagnetic Therapy, and Others

[H4]Interventions

Five studies[22,27,32,36,37] were identified which presented effects of non-exercise interventions; these included whirlpool therapy,[22] graded motor imagery ,[27] light-therapy,[32] oedema focused therapy involving use of compression glove,[36] and computer-regulated brush machine therapy[37] Comparisons were hot towel therapy,[22] home-based exercise,[27] physical therapy,[36] standard occupational therapy,[37] and standard care[32] Studies investigating these interventions differed in terms of duration (range: 2-13 weeks; most common: 2 weeks) and frequency of treatment (range: 2-10 sessions per week; most common: 2/3 sessions per week).[22,27,32,36,37] One study did not mention the duration of follow-up.[22]

[H4]Effects on pain

Four out of 5 studies reported pain outcomes after non-exercise/manual therapy treatments for rehabilitation of wrist fracture.[22,27,32,36] Significant effects on pain were seen for graded motor imagery, light therapy and compression gloves (after 2-, 4- and 8-weeks post-intervention),[27,32,36] but not for whirlpool therapy,[22] hot towels,[22] and computerized brush therapy[37] compared to controls. Studies trialed different treatments and controls making comparisons regarding effectiveness difficult across studies.

[H4]Effects on function

Four out of 5 studies assessed the effects of other non-exercise treatments after wrist fracture.[22,27,36,37] Of these, only 1 found no significant difference between its 2 treatment arms for functional outcomes.[36] Improvements in function following rehabilitation were found with graded motor imagery,[27] occupational therapist-led computer-aided brush machine,[37] and compression glove[36] compared to function in control arms. However, positive findings were associated with non-patient reported outcome measures and limited to the immediate short-term, post-intervention period (ie, 7-15 days) indicating possible selective outcome reporting and no true clinically significant effect on functional disability after wrist fracture.[32] Functional disability as measured using grip strength was not significantly different for standard brush occupational therapy versus computer-regulated brush therapy[37] in the longer term. In summary, the effects of other non-exercise therapy for improving function following wrist fracture remains equivocal.

[H3]Complications

Of the 21 studies, 15 neither reported or investigated complications following treatment of wrist fracture as part of their trials[9,23,25,26,28,31–33,37,41] Of those remaining (n = 6), reporting of onset (timing) and/or duration of symptoms of complications after wrist fracture was limited. Complex regional pain syndrome (CRPS) was the most commonly reported complications (n = 4 studies) with 10% to 15.4% CRPS overall incidence.[23,24,26,32] Participants in the control arms of these studies were reported to be most affected by this complication, however the control arm intervention varied widely (eg, range-of-motion exercises, physical therapist-led exercises, combined physical therapist-led exercises and cryotherapy). Other listed complications included residual pain or stiffness necessitating further interventions,[26,35,40] carpal tunnel syndrome,[24] suboptimal osteosynthesis,[26] transient nerve dysfunction,[26] trigger finger,[24,26] adhesive capsulitis,[23,24,26,32] superficial wound infection,[26] Dupuytren contracture,[26] scar problems,[26] and peripheral nerve decompression.[26] On average across studies, a 10% rate of complications (including CRPS) were reported and there was no indication of statistical difference between intervention and control arms. Incidence of complications were not reported as treatment related but studies were generally underpowered to accurately investigate the relationship between treatment effect and the incident and outcomes of complications.

[H2]Moderators of Treatment Effect Following Wrist Fracture

Two studies investigated factors assessed pre-randomization through moderation or subgroup analysis as part of an a priori defined hypothesis regarding effect moderation.[29,37] Interventions for which moderating factors were identified included exercise therapy as part of multimodal physical therapy,[29] and occupational therapy with computer-regulated brush therapy.[37] Table 1 shows a summary of how these 2 studies performed when considered against the Pincus criteria for the identification of moderators.[20] An outline of suggested (potential) moderators and the supporting exploratory evidence base is presented in Table 2. No study provided a methodologically valid and statistically confirmed moderation of effect for rehabilitation after wrist fracture.

Age >55 years, sex (female), and patient attitude towards computers were investigated as potential moderators of treatment effect. Jarus et al investigated attitude towards computers, using appropriate statistical methods, but the results showed no significant moderation of the effect of computer-regulated brush therapy by a positive attitude towards computers.[37] Sample size however was very small (n = 47 in total). The potential influence of older age was mentioned by the authors, but this was not investigated as most participants were older adults. Ratajczak et al explored the possible role of age and sex on the effectiveness of a rehabilitation package with massage (compared to no massage), using descriptive statistics to present improvement in outcomes in age and sex subgroups, and within each treatment arm.[29] Subgroup effects (between treatment arms) were not presented, and interaction was not tested. The results showed similar outcomes across all subgroups and did not provide evidence of moderation by age or sex of the effect of adding massage, but sample size is again small (n = 40 in total).

Additional factors which were not formally investigated using subgroup/moderation analysis, but suggested (eg, in the discussion section of other studies) to be potential moderators of the effect of rehabilitative interventions for wrist fracture included: eg, functional impairment before fracture,[31] malunion at 6 weeks after fracture,[31] high level of pain at baseline comminution and joint involvement in fracture,[25,31,35] duration of immobilization,[24,26,30,31,38] frequent falls,[28,29,32] low adherence to prescribed treatments,[28,34,40] depression,[9] and low patient expectations (Tab. 3).[31,37,40]

[H1]Discussion

This systematic review synthesized evidence concerning the effectiveness of rehabilitation following wrist fracture. Importantly, it also aimed to summarize evidence for moderators or potential moderators of the effects of rehabilitative treatments following wrist fracture. Findings generally indicate modest improvement in patient outcomes. We found little evidence for the effectiveness of rehabilitation compared to 'usual care' control arms, as all included studies involved active treatment intervention protocols compared against each other in many different ways and combinations. Rehabilitative treatments including electromagnetic therapies and whirlpool were not shown to have a significant effect for improving pain and function following wrist fracture. Though some studies involving exercise/manual therapy as part of a physical therapist-led intervention showed beneficial effects for pain and function, estimates were small and may not be clinically important.

The optimum time for mobilization is yet to be determined but in studies where participants begin physical therapy rehabilitation as early as 2 weeks post-surgical reduction of fracture, beneficial effects for function in the short- and long-term were found. Home exercises in combination with fewer supervised therapist-led sessions were found to lead to similar effects on patient outcomes compared to fully supervised, facility-based exercise rehabilitation sessions (in the short term up to 6 months). However, adherence was variable and not well reported for most studies. It is therefore important that clinicians consider how to optimize engagement and adherence when designing rehabilitative treatment protocols for wrist fracture patients.

To our knowledge, this is the first systematic review to extract and summarize evidence for moderators of the effects of conservative treatments for wrist fracture. Only 2 studies investigated possible effect moderation by age (>55 years old), sex (female) or patient attitude, with only 1 study using appropriate statistical methods, but results suggested there was no influence of these factors on the effects of rehabilitation after wrist fracture. It must be noted however that both trials were very small (less than 30 patients per intervention arm) and not powered to detect interaction. Variation in the effects of rehabilitative treatments following wrist fracture are possibly dependent on a wider range of factors which have yet to be investigated formally in sufficiently powered randomized trials. Earlier reports in this field[42,43] have suggested a possible influence of age, sex, patient motivations/attitude or treatment expectations on outcome of wrist fracture, but such evidence on the prognostic value of these factors does not necessarily mean they can also predict a differential effect of treatment. Furthermore, methodological limitations in the conduct and reporting of results from available studies has limited the strength of evidence for effect moderation. All the potential moderators of treatment effect identified in this review are yet to be examined across large, adequately powered, RCTs. Most of the studies proposing potential moderators of treatment response did not formally investigate moderation, including testing of interaction or adequately presenting subgroup effects. As yet, evidence for moderators of treatment effect following wrist fracture is therefore lacking.

[H2] Implications for Future Research and Practice

Based on currently available evidence, effectiveness of current rehabilitation protocols after wrist fracture is limited; and evidence for effect moderators is lacking as currently available trials are not large enough to produce data on sub-group effects with sufficient precision. To aid clinical practice and optimize effects of rehabilitation after wrist fracture, potential moderators need to be investigated in large trials or meta-analysis using individual participant data. Furthermore, the heterogenous nature of fractures and treatments as reported in current literature makes it difficult to draw conclusions about optimal timing of mobilization. The reporting of rehabilitative interventions could be improved, including key features such as duration, dose or intensity, mode of delivery, and monitoring using for example prescriptions in the TIDieR checklist[44]. This

will not only ensure adequate, homogeneous reporting essential for impactful evidence synthesis but will also aid research design and practice where rehabilitative needs of patients after wrist fracture are closely matched with elements and processes essential to the intervention.

[H2]Strengths and Limitations

We have conducted a detailed systematic review of evidence using a comprehensive search of multiple databases, as well as considering grey literature. Although we considered articles that had been translated into the English language,[29] we excluded 3 articles that may have met our inclusion criteria due to lack of available translations (Fig. 2). We used robust systematic review methods in line with established guidance including 2 independent reviewers for risk of bias and data extraction. Unfortunately, we were unable to conduct a meta-analysis due to insufficient data from studies both comparing the same interventions and using similar outcome measures. We acknowledge a generally low methodological quality among included studies. For instance, we found inconsistencies in reporting of the design, conduct and results of many of the included trials, which may have affected study results. Limitations included differences in baseline characteristics, treatment of control and intervention arms, and low sample sizes.

[H1]Conclusion

Evidence for the effectiveness of most rehabilitative treatments for reducing pain and improving function following wrist fracture is less than optimal. Moderation of the effects of exercise or occupational interventions on functional outcomes after wrist fracture by age (>55 years), sex (being female), or patient attitude/expectations of treatment could not be confirmed. However, there is very little evidence based on formal, high quality moderation analysis for these factors and there will be a need for these to be properly investigated in future pragmatic trials. This will be a first important step to more closely match the rehabilitative needs of patients with wrist fracture.

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Systematic Review Registration

This study was registered a priori on the international prospective register of systematic reviews (PROSPERO) (CRD4201810776).

Disclosure

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

[H1]References

1. Court-Brown CM, Clement ND, Duckworth AD, Biant LC, McQueen MM. The changing epidemiology of fall-related fractures in adults. Injury. 2017 Apr;48(4):819–24.

2. Baron JA, Karagas M, Barrett J, Kniffin W, Malenka D, Mayor M, et al. Basic Epidemiology of Fractures of the Upper and Lower Limb among Americans over 65 Years of Age: Epidemiology. 1996 Nov;7(6):612–8.

3. Ioannidis G, Flahive J, Pickard L, Papaioannou A, Chapurlat RD, Saag KG et al. Non-hip, non-spine fractures drive healthcare utilization following a fracture: the Global Longitudinal Study of Osteoporosis in Women (GLOW). Osteoporos Int, 2013. 24(1): p. 59-67.

4. Nellans KW, Kowalski E, Chung KC. The Epidemiology of Distal Radius Fractures. Hand Clinics. 2012 May;28(2):113–25.

5. Szekeres M, MacDermid JC, Birmingham T, Grewal R, Lalone E. The Effect of Therapeutic Whirlpool and Hot Packs on Hand Volume During Rehabilitation After Distal Radius Fracture: A Blinded Randomized Controlled Trial. Hand (New York, N,Y). 2017 May;12(3):265–71.

6. Gong HS, Song CH, Lee YH, Rhee SH, Lee HJ, Baek GH. Early Initiation of Bisphosphonate Does Not Affect Healing and Outcomes of Volar Plate Fixation of Osteoporotic Distal Radial Fractures. Journal of Bone and Joint Surgery. 2012 Oct 3;94(19):1729–36.

7. Sabesan VJ, Valikodath T, Childs A, Sharma VK. Economic and social impact of upper extremity fragility fractures in elderly patients. Aging Clin Exp Res. 2015 Aug;27(4):539–46.

8. Borgström F, Karlsson L, Ortsäter G, Norton N, Halbout P, Cooper C, et al. Fragility fractures in Europe: burden, management and opportunities. Arch Osteoporos. 2020 Dec;15(1):59.

9. Filipova V, Lonzarić D, Jesenšek Papež B. Efficacy of combined physical and occupational therapy in patients with conservatively treated distal radius fracture: randomized controlled trial. Wien Klin Wochenschr. 2015 Dec;127(S5):282–7.

10. Kristiansen TK, Ryaby JP, McCABE J, Frey JJ, Roe LR. Accelerated Healing of Distal Radial Fractures with the Use of Specific, Low-Intensity Ultrasound. A Multicenter, Prospective, Randomized, Double-Blind, Placebo-Controlled Study*: The Journal of Bone & Joint Surgery. 1997 Jul;79(7):961–73.

11. Cheing G, Wan J, Kai Lo S. Ice and pulsed electromagnetic field to reduce pain and swelling after distal radius fractures. Journal of Rehabilitation Medicine. 2005 Nov 1;37(6):372–7.

12. Bong MR, Egol KA, Leibman M, Koval KJ. A Comparison of Immediate Postreduction Splinting Constructs for Controlling Initial Displacement of Fractures of the Distal Radius: A Prospective Randomized Study of Long-Arm Versus Short-Arm Splinting. The Journal of Hand Surgery. 2006 May;31(5):766–70.

13. Kraemer HC, Wilson GT, Fairburn CG, Agras WS. Mediators and Moderators of Treatment Effects in Randomized Clinical Trials. Arch Gen Psychiatry. 2002 Oct 1;59(10):877.

14. MacDermid JC, Roth JH, Richards RS. Pain and disability reported in the year following a distal radius fracture: a cohort study. BMC Musculoskelet Disord. 2003;4:24.

15. Meena S, Sharma P, Sambharia A, Dawar A. Fractures of distal radius: An overview. J Family Med Prim Care. 2014;3(4):325.

16. Handoll. Rehabilitation for distal radial fractures in adults. Cochrane Database of Systematic Reviews.

17. Hutton. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations.

18. Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. BMJ. 2020 Jan 16;l6890.

19. Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011 Oct 18;343(oct18 2):d5928–d5928.

20. Pincus T, Miles C, Froud R, Underwood M, Carnes D, Taylor SJ. Methodological criteria for the assessment of moderators in systematic reviews of randomised controlled trials: a consensus study. BMC Med Res Methodol. 2011 Dec;11(1):14.

21. McRobert. Identifying potential moderators of first-line treatment effect in patients with musculoskeletal shoulder.

22. Toomey R, Grief-Schwartz R, Piper MC. Clinical Evaluation of the Effects of Whirlpool on Patients with Colles' Fractures. Physiotherapy Canada. 1986;38:280-4.

23. Nguyen A, Vather M, Bal G, Meaney D, White M, Kwa M, et al. Does a Hand Strength–Focused Exercise Program Improve Grip Strength in Older Patients With Wrist Fractures Managed Nonoperatively?: A Randomized Controlled Trial. Am J Phys Med Rehabil. 2020 Apr;99(4):285–90.

24. Dennison DG, Blanchard CL, Elhassan B, Moran SL, Shin AY. Early Versus Late Motion Following Volar Plating of Distal Radius Fractures. Hand (New York, N,Y). 2020 Jan;15(1):125–30.

25. Christensen OM, Kunov A, Hansen FF, Christiansen TC, Krasheninnikoff M. Occupational therapy and Colles' fractures. International Orthopaedics (SICOT). 2001 Mar;25(1):43–5.

26. Clementsen SØ, Hammer O-L, Šaltytė Benth J, Jakobsen RB, Randsborg P-H. Early Mobilization and Physiotherapy Vs. Late Mobilization and Home Exercises After ORIF of Distal Radial Fractures: A Randomized Controlled Trial. JBJS OA. 2019;4(3):e0012.

27. Dilek B, Ayhan C, Yagci G, Yakut Y. Effectiveness of the graded motor imagery to improve hand function in patients with distal radius fracture: A randomized controlled trial. Journal of Hand Therapy. 2018 Jan;31(1):2-9.e1.

28. Hakestad KA, Torstveit MK, Nordsletten L, Risberg MA. Effect of exercises with weight vests and a patient education programme for women with osteopenia and a healed wrist fracture: a randomized, controlled trial of the OsteoACTIVE programme. BMC Musculoskelet Disord. 2015 Dec;16(1):352.

29. Ratajczak K, Plominski J. The Effect of Isometric Massage on Global Grip Strength after Conservative Treatment of Distal Radial Fractures. Pilot Study. *Ortop Traumatol Rehabil*. Jul-Aug 2015;17(4):359-70. doi: 10.5604/15093492.1173378.

30. Tomruk M, Gelecek N, Basçi O, Özkan MH. Effects of early manual therapy on functional outcomes after volar plating of distal radius fractures: A randomized controlled trial. Hand Surgery and Rehabilitation. 2020 May;39(3):178–85.

31. Wakefield AE, McQueen MM. The role of physiotherapy and clinical predictors of outcome after fracture of the distal radius. The Journal of Bone and Joint Surgery British volume. 2000 Sep;82-B(7):972–6.

32. Zlatkovic-Svenda MI, Leitner C, Lazovic B, Petrovic DM. Complex Regional Pain Syndrome (Sudeck Atrophy) Prevention Possibility and Accelerated Recovery in Patients with Distal Radius at the Typical Site Fracture Using Polarized, Polychromatic Light Therapy. Photobiomodulation, Photomedicine, and Laser Surgery. 2019 Apr;37(4):233–9.

33. Wollstein R, Harel H, Lavi I, Allon R, Michael D. Postoperative Treatment of Distal Radius Fractures Using Sensorimotor Rehabilitation. Jnl Wrist Surg. 2019 Feb;08(01):002–9.

34. Magnus CRA, Arnold CM, Johnston G, Dal-Bello Haas V, Basran J, Krentz JR, et al. Cross-Education for Improving Strength and Mobility After Distal Radius Fractures: A Randomized Controlled Trial. Archives of Physical Medicine and Rehabilitation. 2013 Jul;94(7):1247–55.

35. Gutiérrez-Espinoza H, Rubio-Oyarzún D, Olguín-Huerta C, Gutiérrez-Monclus R, Pinto-Concha S, Gana-Hervias G. Supervised physical therapy vs home exercise program for patients with distal radius fracture: A single-blind randomized clinical study. Journal of Hand Therapy. 2017 Jul;30(3):242–52.

36. Miller-Shahabar I, Schreuer N, Katsevman H, Bernfeld B, Cons A, Raisman Y, et al. Efficacy of Compression Gloves in the Rehabilitation of Distal Radius Fractures: Randomized Controlled Study. Am J Phys Med Rehabil. 2018 Dec;97(12):904–10.

37. Jarus T, Shavit S, Ratzon N. From Hand Twister to Mind Twister: Computer-Aided Treatment in Traumatic Wrist Fracture. American Journal of Occupational Therapy. 2000 Mar 1;54(2):176–82.

38. Kuo L-C, Yang T-H, Hsu Y-Y, Wu P-T, Lin C-L, Hsu H-Y, et al. Is progressive early digit mobilization intervention beneficial for patients with external fixation of distal radius fracture? A pilot randomized controlled trial. Clin Rehabil. 2013 Nov;27(11):983–93.

39. Watt CF, Taylor NF, Baskus K. Do Colles' fracture patients benefit from routine referral to physiotherapy following cast removal? Arch Orth Traum Surg. 2000 Jun 26;120(7–8):413–5.

40. Bruder AM, Shields N, Dodd KJ, Hau R, Taylor NF. A progressive exercise and structured advice program does not improve activity more than structured advice alone following a distal radial fracture: a multi-centre, randomised trial. Journal of Physiotherapy. 2016 Jul;62(3):145–52.

41. Maciel JS, Taylor NF, McIlveen C. A randomised clinical trial of activity-focussed physiotherapy on patients with distal radius fractures. Arch Orthop Trauma Surg. 2005 Oct;125(8):515–20.

42. Mehta S. 2012, Predicting Risk for Adverse Outcomes Following Distal Radius Fracture. Ph.D. thesis. McMaster University. https://macsphere.mcmaster.ca/bitstream/11375/12794/1/fulltext.pdf.

43. Jayakumar P, Teunis T, Vranceanu AM, Lamb S, Ring D, Gwilym S. Early Psychological and Social Factors Explain the Recovery Trajectory After Distal Radial Fracture. J Bone Joint Surg Am. 2020 May 6;102(9):788-795. doi: 10.2106/JBJS.19.00100. PMID: 32379119.

44. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ. 2014;348:g1687.

Tables

Table 1. Methodological Assessment of Moderation Analysis[20]

Study	A Priori Hypothesis	Theory-Driven and/or Evidence-Driven Hypothesis	Moderators Measured Prior to Randomization	Valid and Reliable Baseline and Process Factors	Explicit Test of Interaction	Total Score	Level of Moderation Evidence[a]
Jarus et al[37] (2000)	Yes	Yes	Unclear	Unclear	Yes	3	Exploratory
Ratajczak and Plominski[29] (2015)	No	Unclear	Yes	Yes	No	2	Insufficient

[a] Confirmatory = all 5 items met; exploratory = 3+ items met; insufficient = failure to meet 3 items.

Table 2. Summary of Moderators of Treatment Outcomes Following Wrist Fracture

Author (Year)	Interventions Studied	Prognostic Factors Explored or Tested as Potential Moderators	Statistical Analysis Suggestive of Moderation of Treatment Effect	Evidence for Suggested Moderator(s)/Findings of Moderation Analysis on Relevant Outcome	Additional Moderators (Suggested) + Comments	Level of Moderation Evidence (Tab. 1)
Jarus et al[37] (2000)	Use of computer-aided brush machine vs standard occupational therapy brush machine.	Patient attitude towards computers	For each outcome measure (including grip strength as a proxy for function), a 3-way analysis of variance (ANOVA) with repeated measures was performed: 2 (treatment group) x 2 (attitude) x 6 (time) design. Post-hoc tests were then performed to test for significant differences between the means. The level of significance was set at .05.	For function as measured by grip strength: the computer-aided group improved more in grip strength than the control arm starting with the third time point; however, these differences were not significant at any time point. An enhanced interest in the computer-supported intervention was hypothesized to increase the motivation to repeat and continue to exercise and improve hand function. However, the interaction between treatment group and attitude toward computers on outcome was not significant.	Older age was suggested in the discussion section as a potential moderator of the effect of using a computer-aided brush machine compared to a standard machine, but this could not be investigated as most participants were older.	Exploratory
Ratajczak and Plominski[29] (2015)	Isometric massage + rehab package (combined physical therapist-led exercises, cryotherapy, laser- and magnetic field therapy) vs rehab package without massage.	Age, sex	The change in global grip strength was presented for male and female patients and for 2 age groups separately within each treatment arm. No between-group differences were presented within age or sex subgroups, and no interaction tests were performed.	The descriptive analysis shows that younger patients had greater grip strength at baseline than older patients, but improvements with treatment were similar for both age groups in both treatment arms. Grip strength also improved similarly in men and women, regardless of treatment group.	No other candidate moderators were suggested.	Insufficient

Table 3. Other Suggested Moderators (Not Supported by Evidence in Design and Analysis)[a]

Study (Year)	Moderators
Bruder et al[40] (2016)	Participant outcome expectations may affect adherence and improve outcomes. Not hypothesized a priori or planned in analysis.
Christensen et al[25] (2001)	Age, sex, fracture type, dominance. Poor result related to comminution and joint involvement. Occupational therapy may not be suitable for damage of soft tissue structures around the wrist joint. A priori hypothesis was not set or planned for in analysis. Suggested in discussion.
Dennison et al[24] (2020)	Duration of immobilization (onset of rehabilitation). Fracture classification (intra-/extra-articular). Although the late motion group had delayed recovery, there were no long-term (up to 1 y) significant differences in motion, strength, outcome, or pain scores. Hypothesis not set a priori, planned for in analysis but no results and noted in discussion.
Filipova et al[9] (2015)	Age, sex, dominance. Depression Patient expectations and patient-perceived outcome A priori hypothesis was not set or planned for in analysis. Suggested in discussion
Gutierrez-Espinoza et al[35] (2017)	Age, sex, immobilization time, dominance, fracture characteristics (aged >65 y with more needs/complications). **(**Malalignment as a predictor of poor functional outcome). Elderly (>65 y) patients with complications may benefit from professional clinical supervision. May be beneficial to categorize into low and high demand groups. Malalignment is not a predictor of poor functional outcome A priori hypothesis was not set or planned for in analysis. Suggested in discussion
Hakestad et al[28] (2015)	Age, height, weight, BMI, body fat, age of menarche, age of menopause, time since menopause, bisphosphonate, calcium use, past history of fracture, time since fracture, family history of OP, smoking hx, alcohol, education. Multiple fallers may benefit in dynamic balance with an active rehab program. Patient adherence is possibly a moderating factor in active rehab program. Not hypothesized a priori or planned in analysis.
Kuo et al[38] (2013)	Age, sex, fracture type, dominance. External fixator may be deterrent to early mobilization and internal locking plate may be preferable. Not hypothesized a priori or planned in analysis.
Magnus et al[34] (2013)	Age, sex, height, weight; age may be a moderating factor, but was not explored due to the small sample size. Surgical intervention may be a moderating factor, but was not explored due to small sample size. Adherence may be a moderating factor, but was the same level in both arms. Not hypothesized a priori or planned in analysis.
Zlatkovi-Svenda et al[32] (2019)	(Daily home exercises, poor balance control at baseline was associated with a better improvement in outcomes). Poor balance control at baseline. Daily home exercises. Suggested in analysis and discussion.
Tomruk et al[30] (2020)	(Lower age in treatment group could have contributed to increased functional improvement). Lower age. Active joint mobilizations in early postoperative period. Technique: Performing active joint mobilization in a pain-free ROM Suggested in analysis and discussion.

[a] ROM = range of motion; y = year(s).

Figure legends

Figure 1. Full Medline search strategy.

ORDAR - Wrist fracture intervention studies

MEDLINE ran 27.06.18 (Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present)

#	Searches	Results
1	exp Fractures, Bone/	169266
2	fracture$.ti,ab,kw.	229140
3	exp Wrist Joint/	9355
4	Wrist Injuries/	5929
5	Wrist/	8207
6	(radius/ or ulna/ or forearm/ or forearm injuries/) and distal.ti,ab,kw.	4776
7	exp Carpal Bones/	8365
8	(wrist or colles$1 or smith$).ti,ab,kw.	46282
9	(capitate or hamate or lunate or pisiform or trapezium or triquetrum or trapezoid or scaphoid).ti,ab,kw.	9071
10	((radius or radial or ulna$ or forearm$) and distal).ti,ab,kw.	18362
11	1 and (or/3-10)	11861
12	(1 or 2) and (or/3-7)	8242
13	Colles' Fracture/	845
14	((wrist or colles$1 or smith$) adj5 fracture$).ti,ab,kw.	2798
15	((capitate or hamate or lunate or pisiform or trapezium or triquetrum or trapezoid or scaphoid) adj5 fracture$).ti,ab,kw.	2324
16	Ulna Fractures/ and distal.ti,ab,kw.	627
17	radius fracture/ and distal.ti,ab,kw.	3961
18	(((radius or radial or ulna$ or forearm$) adj5 fracture$) and distal).ti,ab,kw.	5604
19	or/11-18	14748
20	randomized controlled trial.pt.	462867
21	controlled clinical trial.pt.	92401
22	randomized.ab.	495994
23	placebo.ab.	189808
24	clinical trials as topic/	183938
25	randomly.ab.	292750
26	trial.ti.	183807
27	or/20-26	1188338
28	exp animals/ not humans/	4467410
29	27 not 28	1095677
30	19 and 29	982

Figure 2. PRISMA flow chart.

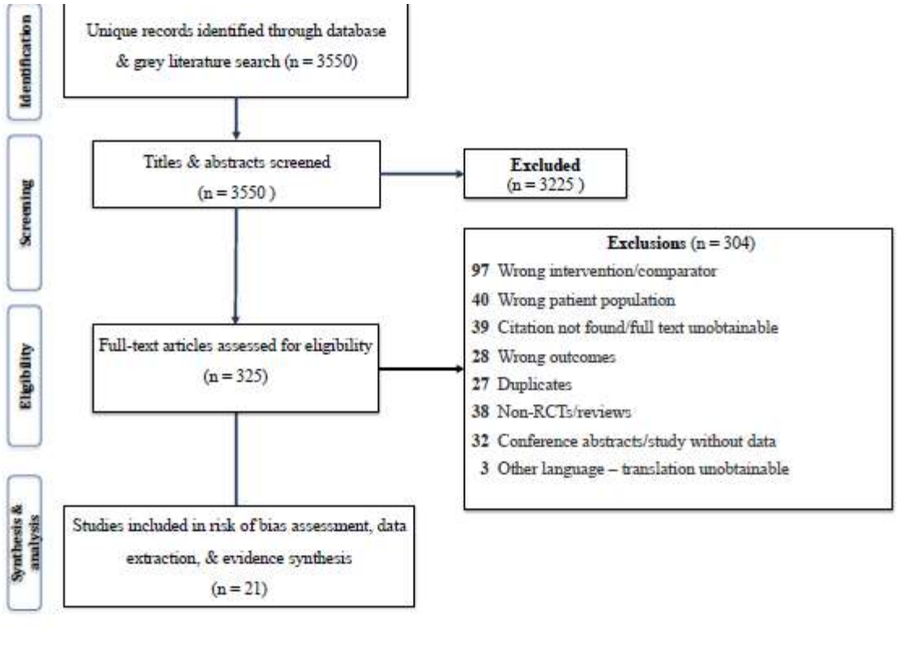

Figure 3. Risk of bias in individual studies.