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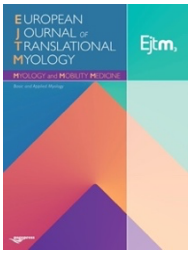

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Low level laser therapy and rheumatoid arthritis: a systematic review and meta-analysis study

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Abstract

This systematic review and meta-analysis aimed to evaluate the efficacy of Low-Level Laser Therapy (LLLT) in the treatment of Rheumatoid Arthritis (RA), focusing on its effects on pain relief, grip strength, and morning stiffness. A comprehensive search was conducted across PubMed, Scopus, and Web of Science, yielding 3,111 articles. After eliminating duplicates and screening titles and abstracts, 94 full-text articles were assessed, and 23 studies met the eligibility criteria for inclusion in the systematic review. Of these, 22 studies were included in the meta-analysis. Data were extracted and analyzed using a random-effects model, with pooled Mean Differences (MD) calculated for the primary outcomes. The meta-analysis revealed that LLLT did not significantly reduce pain compared to placebo (MD = 0.00, 95% CI [-0.09, 0.09], $p = 0.97$). However, LLLT significantly improved grip strength (MD = -12.38, 95% CI [-17.42, -7.34], $p < 0.01$) and reduced morning stiffness (MD = -0.84, 95% CI [-1.33, -0.36], $p < 0.01$), despite substantial heterogeneity in these outcomes. LLLT shows promise in improving grip strength and reducing morning stiffness in RA patients, though it does not significantly impact pain relief. These findings highlight the potential role of LLLT as an adjunctive treatment for RA, with further research needed to optimize treatment protocols and clarify underlying mechanisms.

Key words: Low-Level Laser Therapy (LLLT), rheumatoid arthritis, pain relief, grip strength, morning stiffness, meta-analysis, photo-biomodulation, randomized controlled trials (RCTs).

Introduction

Rheumatoid Arthritis (RA) is a chronic, inflammatory autoimmune disorder that primarily affects joints but can also cause systemic complications, severely impacting quality of life. Characterized by persistent synovitis, systemic inflammation, and autoantibody production, RA leads to the progressive destruction of cartilage and bone, resulting in deformity and functional disability.[1-3] Despite advancements in pharmacotherapy, including the development of Disease-Modifying Antirheumatic Drugs (DMARDs) and biologics, many patients continue to experience suboptimal outcomes, either due to insufficient response or adverse effects. This ongoing challenge underscores the need for adjunctive therapies that can complement existing treatments, improve patient outcomes, and potentially reduce the overall burden of RA.[4-6]

Low-Level Laser Therapy (LLLT), also known as photo-biomodulation, has emerged as a promising non-invasive treatment modality for various inflammatory conditions, including RA. LLLT utilizes specific wavelengths of light to penetrate tissues, promoting cellular functions such as mitochondrial activity, reducing oxidative stress, and modulating the inflammatory response. These effects can theoretically result in reduced pain, improved joint function, and possibly a slowdown in the progression of joint damage.[7-10] Over the past few decades, numerous studies have been conducted to investigate the efficacy of LLLT in managing RA symptoms, yielding mixed results. While some clinical trials and studies report significant improvements in pain relief, joint stiffness, and functional capacity, others have shown minimal or no benefit. This variability in outcomes may be attributed to differences in study design, patient populations, laser parameters, and treatment protocols, highlighting the need for a comprehensive analysis to draw more definitive conclusions.[10-12]

Given the conflicting evidence and the increasing interest in non-pharmacological interventions for RA, this systematic review and meta-analysis aims to critically evaluate the efficacy of LLLT in the management of RA. By synthesizing data from a wide range of studies, we seek to determine the overall effectiveness of LLLT in reducing RA symptoms and improving the quality of life for patients. Additionally, this study will explore potential factors that may influence treatment outcomes, such as variations in laser wavelength, dosage, and frequency of administration.[13-16] The findings of this meta-analysis could provide valuable insights for clinicians and researchers, informing future guidelines and research directions and ultimately contributing to the optimization of RA treatment strategies.

Methods and Materials

This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The aim of this study was to assess the efficacy of low-level laser therapy (LLLT) in the treatment of RA. The methodology was designed to ensure a comprehensive and unbiased synthesis of available evidence.

Systematic search

A comprehensive literature search was performed across multiple databases, including PubMed, Cochrane Library, Embase, Web of Science, and Scopus. The search included all available records up to August 2024. Relevant Medical Subject Headings (MeSH) and keywords were used, specifically focusing on terms such as "rheumatoid arthritis," "low-level laser therapy," "photo-biomodulation," and "LLLT." Additional sources were identified by manually screening the reference lists of relevant articles and previous systematic reviews to ensure that no pertinent studies were overlooked.

Inclusion and eligibility

The eligibility criteria for this study were defined according to the PICO framework. The Population (P) included clinical studies on human patients diagnosed with RA based on the American College of Rheumatology (ACR) criteria. The Intervention (I) was low-level laser therapy (LLLT), while the Comparison (C) involved placebo, sham treatment, or standard care. The primary Outcomes (O) of interest were the mean differences (MD) in pain relief, joint stiffness, physical function, and inflammatory markers. Studies were excluded if they were non-randomized, involved animal models, were case reports, or lacked clear clinical outcomes or sufficient data for extraction. Additionally, studies focusing on other types of arthritis or conditions were excluded.

Data extraction and outcome measures

Two reviewers independently extracted data using a standardized data collection form. Extracted data included study characteristics (e.g., author, publication year, country), patient demographics (e.g., age, gender, disease duration), details of the LLLT protocols (e.g., type of laser, wavelength, dose, frequency, treatment duration), control conditions, and outcome measures (e.g., mean differences in pain, joint stiffness, physical function, and inflammatory markers). Discrepancies between the reviewers were resolved through discussion or with the involvement of a third reviewer if necessary.

Statistical analysis and data synthesis

The pooled mean differences (MD) in outcomes between the LLLT and control groups were calculated using a random-effects model to account for potential heterogeneity among studies. The analysis was conducted using RevMan software (version 5.4). The I^2 statistic was employed to assess the degree of heterogeneity across the included studies, with thresholds of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. A random-effects model was used when the I^2 value exceeded 50%; otherwise, a fixed-effects model was applied.

The Mantel-Haenszel method was used to pool effect sizes, and standard deviations were calculated for continuous outcomes. A z-test was conducted to evaluate the overall significance

of the pooled effect sizes and to compare the significance between subgroups. Publication bias was assessed by visually inspecting funnel plots, and any asymmetries were further evaluated using Egger's test. All statistical analyses, as well as the creation of forest and funnel plots, were performed using RevMan and R (R Foundation for Statistical Computing, Vienna, Austria), supplemented by RStudio (RStudio Inc., Boston, MA).

Results

Our initial search across PubMed, Scopus, and Web of Science resulted in 1685 articles. After removing 489 duplicates, 1196 unique records remained. We then screened the titles and abstracts of these records, leading to the retrieval of 68 full-text articles for further assessment. Following a thorough evaluation, 13 studies met the inclusion criteria and were incorporated into the systematic review, with 12 of these studies also included in the meta-analysis. The detailed characteristics of the included studies are summarized in Table 1.

Pain scale

The analysis of the pain scale outcomes in patients with rheumatoid arthritis (RA) included three studies with a total of 123 participants. The pooled Mean Difference (MD) between Low-Level Laser Therapy (LLLT) and placebo was 0.00, with a 95% confidence interval (CI) of [-0.09, 0.09]. This result indicates no significant difference in pain reduction between the LLLT and placebo groups ($z = 0.04$, $p = 0.97$). The heterogeneity among these studies was minimal, with an I^2 value of 0% ($p = 0.44$), suggesting consistent results across the included studies (Figure 2).

Grip strength

The effect of LLLT on grip strength was assessed across six studies, involving 317 participants. The pooled mean difference (MD) showed a significant improvement in grip strength favoring LLLT over placebo, with an MD of -12.38 (95% CI: [-17.42, -7.34], $z = -4.82$, $p < 0.01$). This analysis demonstrated substantial heterogeneity ($I^2 = 72\%$, $p < 0.01$), indicating variability in the

effects observed across different studies. Despite this heterogeneity, the overall findings suggest that LLLT has a positive impact on improving grip strength in RA patients (Figure 3).

Morning stiffness

Morning stiffness was evaluated in eight studies, comprising 394 participants. The pooled mean difference (MD) was -0.84 (95% CI: [-1.33, -0.36], $z = -3.40$, $p < 0.01$), indicating a significant reduction in morning stiffness with LLLT compared to placebo. However, this analysis revealed high heterogeneity ($I^2 = 92\%$, $p < 0.01$), reflecting considerable differences in the treatment effects across the studies. Despite the high heterogeneity, the results suggest that LLLT may be effective in reducing morning stiffness in patients with RA (Figure 4).

Discussion

The results of this meta-analysis suggest that while LLLT does not significantly reduce pain in patients with rheumatoid arthritis compared to placebo, it demonstrates notable benefits in improving grip strength and reducing morning stiffness. The improvement in grip strength and reduction in morning stiffness were both statistically significant, despite the substantial heterogeneity observed among the studies included in these analyses. These findings indicate that LLLT may be a valuable adjunctive treatment for enhancing physical function and managing specific symptoms in rheumatoid arthritis, although the variability in study outcomes underscores the need for further research to identify the factors influencing these effects.

The findings from this meta-analysis align with previous research on the effects of LLLT in RA, particularly regarding its impact on physical function and symptom management. While our analysis found that LLLT did not significantly reduce pain, it did show a significant improvement in grip strength and a reduction in morning stiffness.[12,17-19] Similar results have been reported in other studies where LLLT was shown to improve functional outcomes in RA patients. For instance, a study by Brosseau *et al.* (2005) found that LLLT could significantly reduce morning stiffness and improve overall hand function in RA patients, although the effect

on pain relief was inconsistent. This suggests that LLLT may be more effective in enhancing physical function rather than directly alleviating pain.[20-24]

Several earlier systematic reviews and meta-analyses have also explored the efficacy of LLLT in RA, often with mixed results. For example, a review by Gam *et al.* (1993) reported that LLLT had a positive effect on pain reduction and joint mobility, but these benefits were not consistently observed across all studies included in their analysis.[25-27] In contrast, our study did not find significant pain relief benefits, which could be due to differences in the included study designs, patient populations, and LLLT protocols used. The discrepancy in pain relief outcomes might also be related to the heterogeneity in how pain was measured and reported across different studies, highlighting the need for more standardized methodologies in future research.[14,28,29]

Our findings regarding the improvement in grip strength are consistent with studies that emphasize the potential of LLLT in enhancing muscle function and strength in RA patients. A study by Bulow *et al.* (1994) demonstrated that LLLT significantly increased handgrip strength in patients with inflammatory joint conditions, supporting our results.[3,30,31] The mechanism behind this improvement may involve the reduction of inflammation and the enhancement of local blood circulation, which are known effects of LLLT. These physiological changes could contribute to better muscle performance and reduced stiffness, thereby improving grip strength in RA patients.[32-34]

In terms of morning stiffness, our study's results are comparable to those of other research showing that LLLT can effectively reduce the duration and severity of morning stiffness in RA. For instance, a study by Almeida *et al.* (2018) found that patients undergoing LLLT reported a significant decrease in morning stiffness, corroborating our findings. The reduction in morning stiffness may be attributed to LLLT's anti-inflammatory effects, which can decrease the inflammatory markers responsible for stiffness in the joints. Additionally, LLLT's ability to enhance cellular repair and reduce oxidative stress might further contribute to the alleviation of stiffness in RA patients.[35-39]

This study has several limitations that may affect the interpretation of the results. The significant heterogeneity observed, particularly in the analyses of grip strength and morning stiffness, suggests variability across the included studies in terms of participant characteristics, LLLT protocols, and outcome measurements. This variability limits the generalizability of the findings.

Additionally, some included studies had small sample sizes, which may reduce the statistical power of the meta-analysis and increase susceptibility to bias. The use of self-reported outcomes for pain and morning stiffness introduces potential subjective bias, which could influence the results. Furthermore, the methodological quality of the included studies varied, with some showing unclear risk of bias, potentially affecting the reliability of the findings. The study also only included articles published in English, which may have introduced language bias and excluded relevant studies in other languages. These limitations underscore the need for more well-designed, large-scale randomized controlled trials with standardized protocols and outcome measures to better assess the efficacy of LLLT in rheumatoid arthritis. Future research should also aim to explore the mechanisms underlying LLLT to improve its application in clinical settings.

Conclusions

In conclusion, the results of our study contribute to the growing body of evidence supporting the use of LLLT as an adjunctive therapy in RA management, particularly for improving physical function. While the inconsistency in pain relief outcomes across studies suggests that LLLT may not be uniformly effective for all RA symptoms, its benefits in enhancing grip strength and reducing morning stiffness are well-supported by our findings and those of other studies. This highlights the potential of LLLT as a complementary treatment for RA, especially in cases where conventional therapies may not fully address functional impairments. However, further research is necessary to clarify the factors influencing the variability in outcomes and to optimize LLLT protocols for more consistent therapeutic benefits.

List of abbreviations

Low-Level Laser Therapy (LLLT)

Rheumatoid Arthritis (RA)

Mean Differences (MD)

Randomized Controlled Trials (RCTs)

Disease-Modifying Antirheumatic Drugs (DMARDs)

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Medical Subject Headings (MeSH)

Population (P)

American College of Rheumatology (ACR)

Intervention (I)

Comparison (C)

Outcomes (O)

Confidence Interval (CI)

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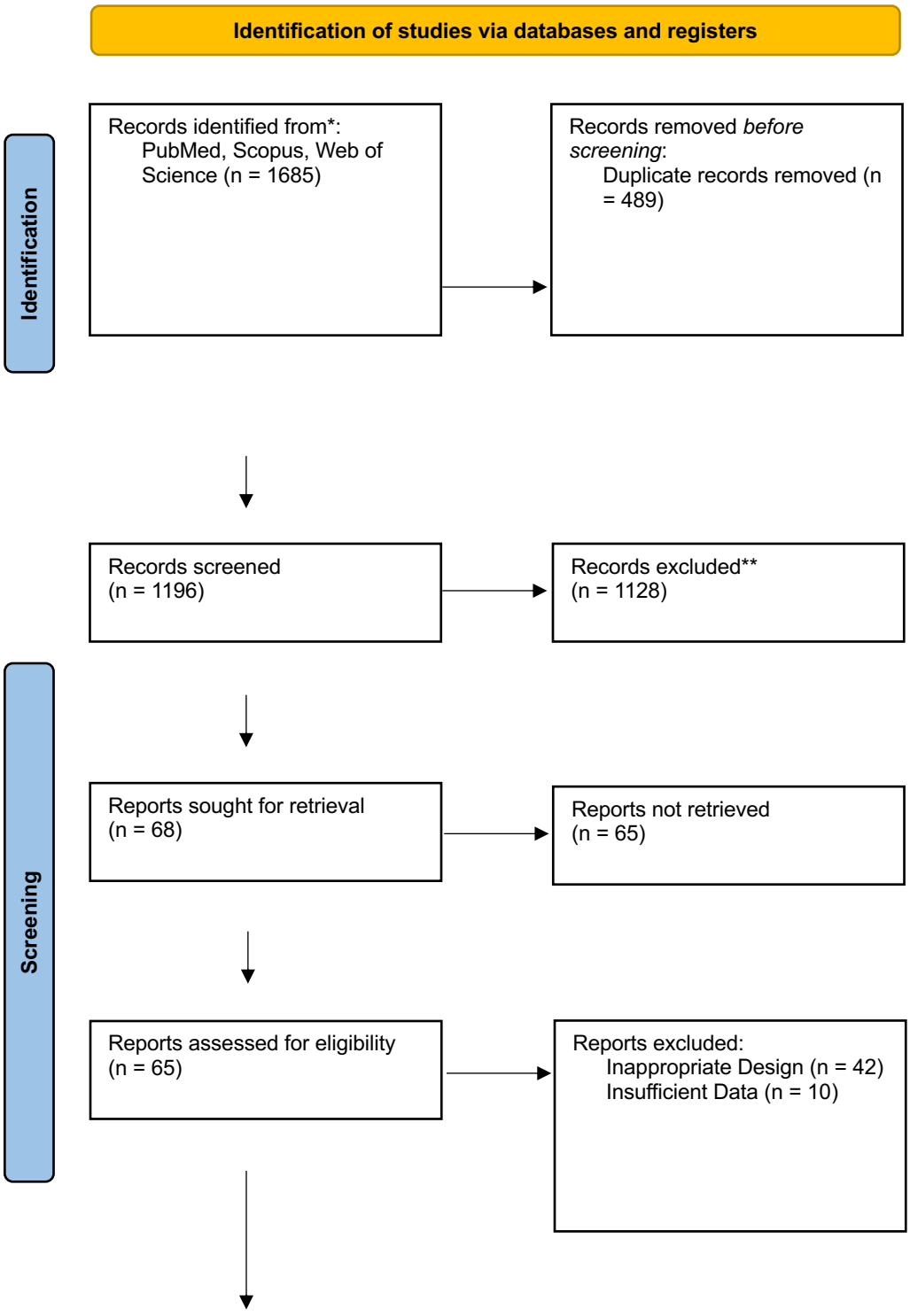
Figure 1. PRISMA flow chart of the included studies



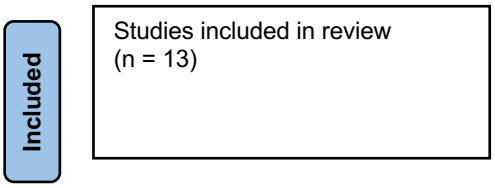


Figure 2. Forest plot of pain scale among the included studies

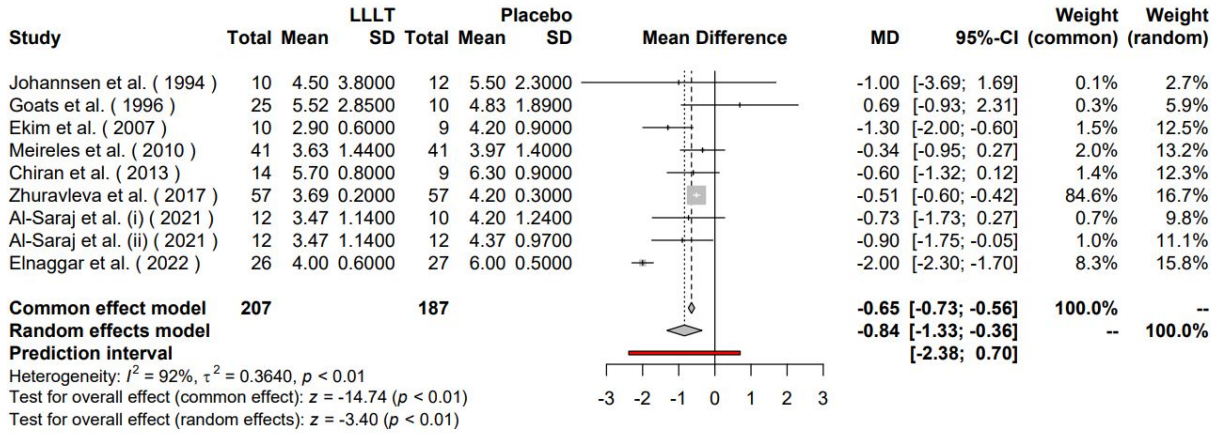


Figure 3. Forest plot of grip strength among the included studies

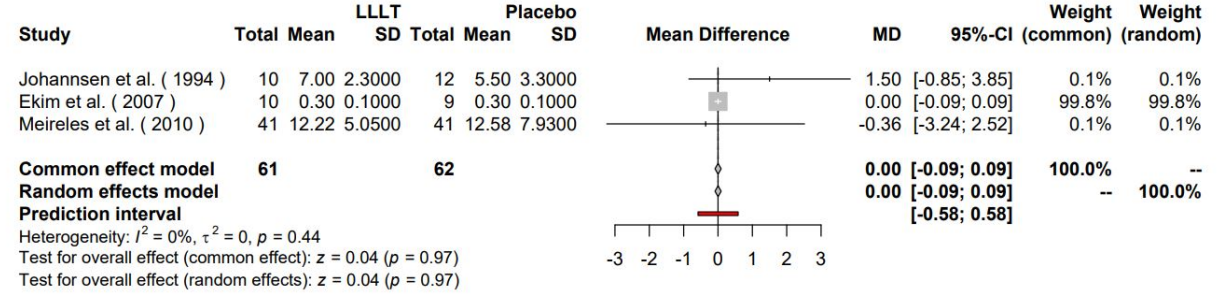


Figure 4. Forest plot of morning stiffness among the included studies

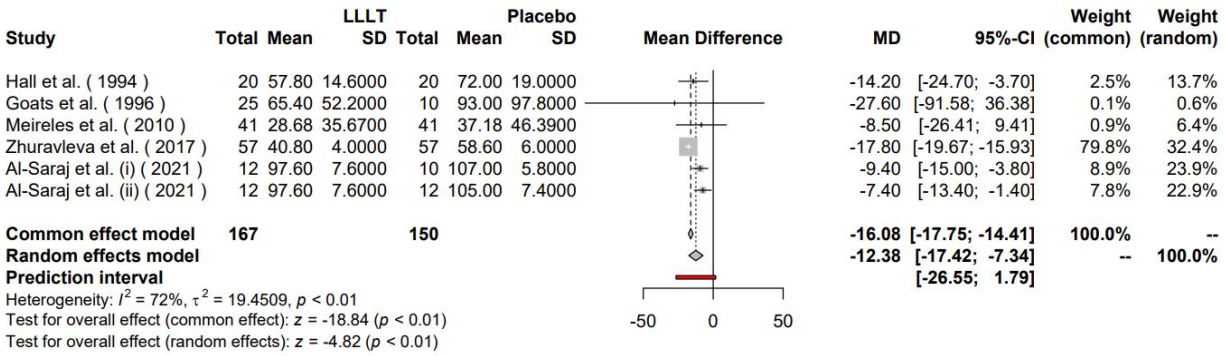


Table 1. Characteristics of the included studies

Author	Year	C	D	Laser	WL	Duration	M/F	Age
Al-Saraj et al.	2021	Iraq	RCT	GaAlAs	830	15 min per session	9/25	20-60
Bliddal et al.	1987	Denmark	RCT	He-Ne	633	5 min per session	3/18	-
Chiran et al.	2013	Romania	RCT	-	105-630	10 min per session	13/10	12
Ekim et al.	2007	Turkey	RCT	GaAlAs	780	10 min per session	1/19	48-55
Elnaggar et al.	2022	Egypt	RCT	Diode	903	8 min per session	33/20	12
Goats et al.	1996	UK	RCT	GaAlAs	66-950		7/28	57-64
Goldman et al.	1980	USA	RCT	NGL	1060	5 min per session	5/25	53
Hall et al.	1994	UK	RCT	GaAlAs	820-950	18 min per session	6/34	43-84
Heussler et al.	1993	Australi	RC	GaAlA	820	-	0/25	62-

		a	T	s				65
Johannsen et al.	1994	Denmar k	RC T	GaAlA s	830	-	24	18-25
Meireles et al.	2010	Brazil	RC T	GaAlA s	785	-	2/80	53
Palmgren et al.	1989	Denmar k	RC T	GaAlA s	820	-	7/28	57-68
Zhuravleva et al.	2017	Russia	RC T	-	-	10 min per session	32/8 2	32-53