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Effects of electromagnetic therapy on proprioception in a rodent animal model of rheumatoid arthritis

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Abstract

Introduction. This study aimed primarily to investigate the effect of a PEMF on proprioception in terms of mechanoreceptor number and function and secondarily to assess the gait quality (sciatic function index) and arthritis severity (paw volume and body weight) in adjuvant-induced arthritis (AIA) RA model.

Methods. Twenty-eight healthy adult male Wistar rats were randomly divided into 3 groups: (I) RA experimental model treated with a PEMF (10 animals), (II) positive control (10 animals), and (III) negative control (8 animals). Group I was exposed to a PEMF (0.3 mT 1 h/day for 2 weeks), while Groups II and III were placed in the same setup, except that the PEMF was turned off. The proprioceptive function [as tactile response (TR) / hopping response (HR) / forelimb placing test (FPT)], paw volume (PF), and mechanoreceptor numbers were then tested.

Results. There was a significant preservation of mechanoreceptor numbers and proprioception in group I compared to group II, as follows: the number of Ruffini corpuscles mechanoreceptors ($p = 0.007$) and TR on days 9 and 14 ($p = 0.002$, 0.012, respectively) with no significant difference compared to group III. Also, PV decreased significantly in group I relative to group II ($p = 0.01$) with no significant difference for group III.

Conclusions. PEMF significantly preserved proprioception receptors and function and decreased inflammation severity in the AIA-RA model.

Key words: electromagnetic therapy, mechanoreceptor, proprioception, fascia, Freund's adjuvant, rheumatoid arthritis

Introduction

RA patients have an increased risk of falling [1]a total of 289 patients with RA, ages 24–85 years, were followed using quarterly fall diaries to report falls. At the baseline, medical data such as RA disease duration and Disease Activity Score (DAS28CRP which is commonly complicated by fractures due to the presence of RA-induced osteoporosis [2]. This problem can be attributed to muscle weakness (due to inactivity and treatment with steroidal anti-inflammatory drugs), joint pathology, or decreased visual acuity due to steroid-induced cataract or drug side effects [3]. However, its' most obvious cause is defective proprioception [4]. Proprioception defect can be attributed directly to peripheral neuropathy (axonal degeneration and demyelination) and decreased mechanoreceptor numbers [5] and indirectly to pain and inflammation [6]. As RA treatments' main concern is to control pain and inflammation, balance assessment and management are usually ignored [7]. One of the most popular methods to enhance balance is exercise, as it can decrease fatigue, pain, depression, and walking time [8], but eccentric or high-intensity exercise can produce pain and delayed onset muscle soreness [9]. Moreover, RA patients' tolerance of exercise is affected by fatigue, so it often cannot be done appropriately and continuously [8]. One of the potential alternatives is a pulsed electromagnetic field (PEMF), which is a passive, non-invasive, safe, and easy therapeutic intervention for treating painful and inflammatory conditions [10]. Moreover, it provides a protective effect for bone and cartilage in RA equal to diclofenac sodium but without its adverse side effects [11]. To assess this defect and a potential treatment, we utilise an RA animal model that is commonly used for this purpose [12]. The most common models are; (1) Type II collagen arthritis: which allows a short duration of testing (7 days) and is unilateral [13]; (2) Antigen arthritis: which simulates acute localised inflammation in 1 or 2 joints [14]; (3) Adjuvant-induced arthritis (AIA): which is a whole-body model that affects all joints and organs and resembles all phases of RA (remission phase on days 1 to 9, relapse phase on days 10 to 12, and chronic and deformity phase on days 20 to 60), and has good reproducibility and reliable onset and progression [12]. Although several tissues are affected by mechanoreceptor depletion, fascia has a severe affection. Thoracolumbar fascia (TLF) is the largest fascia in the body of both humans and rats [15] and it binds with large muscles (latissimus dorsi, gluteus maximus, and transversus abdominis) that play a key role in postural stability [16]. It also plays a central role in proprioception, as it is always under tension and is richly innervated by mechanoreceptors [17]. Although TLF has a similar rich innervation in humans and rats, studies concerning its function and pathology are still lacking [15].

This study aims primarily to provide an answer to the question 'Does a PEMF increase proprioception in terms of mechanoreceptor number and/or function in an AIA model of RA?' and secondarily to answer the question 'Does a PEMF change gait quality or arthritis severity in an AIA model of RA?'.

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Subjects and methods

Animals

Twenty-eight healthy adult male Wistar rats weighing 200–250 g were procured from a local animal facility four days before the experiment to acclimate to the new location. Housing, care, and experimental procedures were approved by the Institutional Animal Care and Use Committee, Cairo University (approval number: CU/III/F/81/17).

Pulsed electromagnetic field (PEMF)

A PEMF was generated within a custom-made solenoid carrying a current of 18 amperes at 50 Hz from the mains supply (220–230 volts) via a Variac transformer. The solenoid consisted of 320 turns of electrically insulated 0.8 mm copper wire that is wrapped around a copper cylinder of 2 mm thickness, 42 cm diameter, and 40 cm length. The cylinder wall was earthed to eliminate static charges. The magnetic field intensity was measured at different locations to confirm a homogenous PEMF inside the solenoid by a Gauss/Tesla probe meter manufactured by Bell Technologies Inc. (Orlando, FL, USA).

Experimental groups

Since there was no data from previous studies with the same outcome measure, a sample of 8–10 animals per group was used [18]. The animals were randomly divided using the MS Excel random number generator function into three groups: (I) RA experimental group (n = 10) which is the RA model that received PEMF therapy of 0.3 mT for 1 h/day at the same time every day, 6 days/week for 2 weeks, (II) positive control (n = 10) which is the RA model that received sham PEMF therapy, and (III) negative control (n = 8) which is the group of normal animals that received sham PEMF therapy. One animal from group II died spontaneously on day 0 before the start of the study.

Induction of adjuvant-induced arthritis (AIA)

AIA was induced by injecting 0.1 ml of Freund's complete adjuvant suspension (Sigma Chemical Co., USA) into the base of the tail of the rats [12], resulting in nerve fibre depletion similar to that found in RA patients [19]. Inflammation onset occurs on days 9–10 post-injection. Treatment was initiated on day 0 (prophylactic model) [20]. This study was ended 14 days after injection, before the development of severe disability and deformity.

Proprioception assessment

A. Proprioception function evaluation

The proprioception function was evaluated on day 9 (onset of disease), and day 14 (end of treatment) [21] as follows:

a. Tactile placing response (Figure 1): with the animal supported in a normal resting posture by the examiner's hand, and the toes of the right foot were flexed. A response that takes more than 10 s is considered no response. The score was calculated as the number of normal responses out of 3 consecutive trials. The response was graded as (3) normal (2) slightly impaired (1) severely impaired (0) absent [21]posture, gait, proprioception, motor function, autonomic function, and nociception.

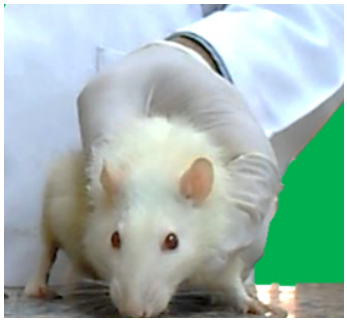

Figure 1. Tactile placing response

b. Hopping response (Figure 2): with the animal supported upright by the examiner's hand, the left foot was lifted off the ground, then the animal's body was moved laterally until the animal hopped with the weight-bearing foot to avoid falling. Foot dragging is considered no response. The score was calculated as the number of normal responses out of 3 consecutive trials [21].

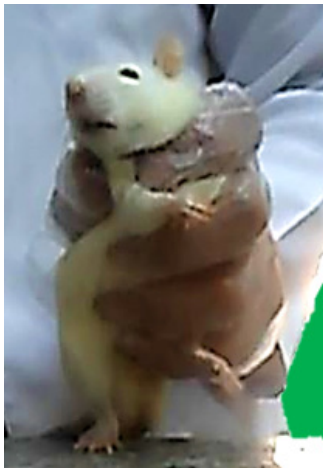

Figure 2. Hopping response

c. Forelimb placing test (Figure 3): The animal (held by its trunk) was positioned parallel to a tabletop and then slowly moved up and down, allowing the vibrissae on the right side to brush along the table's edge. The score was calculated as the number of successful forelimb placements out of 10 consecutive trials [22].

Figure 3. Forelimb placing test

B. Histological examination

Immediately following euthanasia by cervical dislocation, TLF was harvested and kept fully immersed in Krebs-Ringer solution (Ringer solution + glucose for cell survival) at room temperature for less than 24 hours, then stained using a modified gold-chloride method [23] as follows; tissues were immersed in a solution of 3:1 lemon juice to 88% formic acid in darkness for 20 min or until the tissue colour turned trans-

parent. Then, the solution was replaced by a 1% solution of gold chloride, and the container was placed again in darkness for 60 min. Next, the tissues were immersed in a 25% solution of formic acid for 8 hours in darkness (block staining) before being rinsed in 3 changes of 70% ethanol, each for 10 min. The tissues were then placed in glycerol for 24 hours, followed by dehydration and paraffin-embedding according to standard histological procedures. Longitudinal serials of 5 µm sections were cut at a 30 µm sampling rate, three sections were mounted on each glass slide, and three to five slides per specimen were prepared for bright field examination. The slides' labels were concealed and randomly recoded. An average of three examinations of the maximum number of Pacinian and Ruffini corpuscles in each section per (400X) magnification power field were recorded.

Sciatic function index (*SFI*)

SFI is an indicator of the degree of dysfunction of the lower extremity nerve and kinematics (Figure 4), ranging mainly from –100 to zero, where –100 represents full dysfunction and zero represents normal function. The equation of the measurable distances of footprints is [24]:

$$SFI = -38.3\frac{EPL - NPL}{NPL} + 109.5\frac{EPL - NPL}{NPL} + 13.3\frac{EPL - NPL}{NPL} - 8.8$$

where: E – experimental, N – normal, PL – print length, TS – total spread, IT – intermediary toes.

Before testing, the animals were habituated to the walkway and learned to cross it from end to end, which was stimulated by a dark goal box at the opposite end, noise, or another rat being put in the goal box [25]. A higher SFI value indicates a better gait quality.

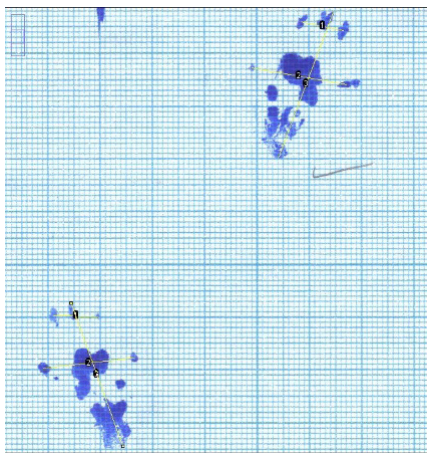

Figure 4. Sciatic function index

Measurement of clinical severity of arthritis

Paw swelling (right paw volume up to the medial malleolus level) was measured using a plethysmometer (water displacement) [26] on day 2 and then on alternate days until day 14. Body weights were recorded on days 0, 9, and 14.

Statistical analysis

All data of primary (proprioceptor number and functional proprioception tests) and secondary (sciatic function index, paw volume, and body weight) outcomes were presented as medians and ranges. Between-group comparisons were performed using the Kruskal–Wallis ANOVA test, followed by the Mann–Whitney test to detect significance between groups. Significant results were then adjusted for multiple comparisons by the Bonferroni test. Within-group comparisons were analysed using Friedman's test, and if significant, it was followed by sign rank to detect changes over time within the same group. For all analyses, the significance level was set at $p < 0.05$. All statistical analyses were performed using SPSS version 26.0 (IBM incorporation, Chicago, IL, USA).

Ethical approval

The research related to human use has complied with all the relevant national regulations and institutional policies, has followed the tenets of the Declaration of Helsinki, and has been approved by by the Institutional Animal Care and Use Committee, Cairo University (approval number: CU/III/F/81/17).

Results

A. Proprioception

Proprioception functional testing: results of between-groups comparisons (Table 1) showed a significant increase in tactile response on day 9 (Figure 5) and day 14 (Figure 6) in group I compared to group II ($p = 0.002$, 0.012, respectively) with no significant difference compared to group III ($p = 0.52$, 0.22, respectively), and a significant increase in hopping response on day 14 (Figure 7) in group I compared to group II ($p = 0.024$) with no significant difference compared to group III ($p \geq 0.99$). There was also a significant decrease in the forelimb placing test on day 9 (Figure 8) in group II compared to group III ($p = 0.02$) with no significant difference between groups I and III ($p = 0.61$). However,

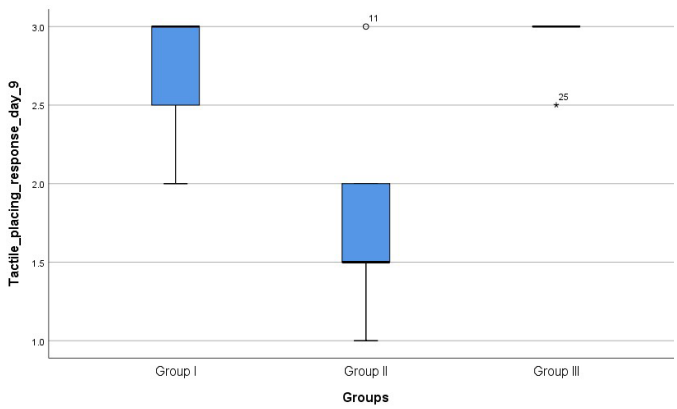

Figure 5. Box plot of between-group comparison of tactile response day 9

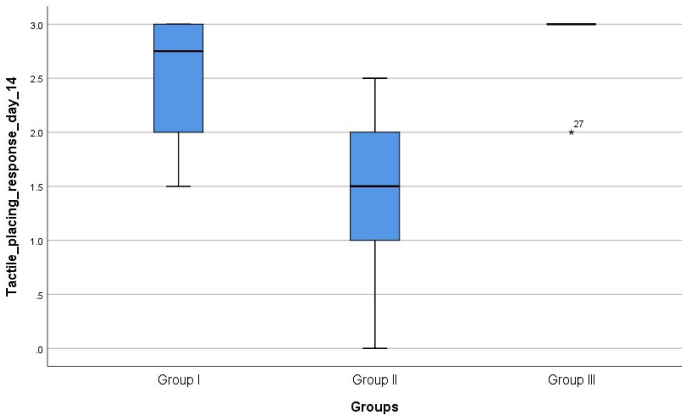

Figure 6. Box plot of between-group comparison of tactile response day 14

Table 1. Results of proprioception functional testing presented as median (minimum-maximum)

Groups		Hopping response day 9	Hopping response day 14	Tactile placing response day 9	Tactile placing response day 14	Forelimb placing test day 9	Forelimb placing test day 14
Group I (*n* = 10)	median	3	3*	3**	2.75***	10	10
	minimum	0	3	2	1.5	9	10
	maximum	3	3.0	3.0	3	10	10
Group II (*n* = 9)	median	3	3	1.5	1.500	10$	10
	minimum	2	0	1	0	8	7
	maximum	3	3	3	2.5	10	10.0
Group III (*n* = 8)	median	3	3	3	3	10	10
	minimum	1	3	2.5	2	10	9
	maximum	3	3	3	3	10	10

* significant increase compared to group II (p = 0.024)
** significant increase compared to group II (p = 0.002)
*** significant increase compared to group II (*p* = 0.012)
$ significant decrease compared to group III (*p* = 0.02)

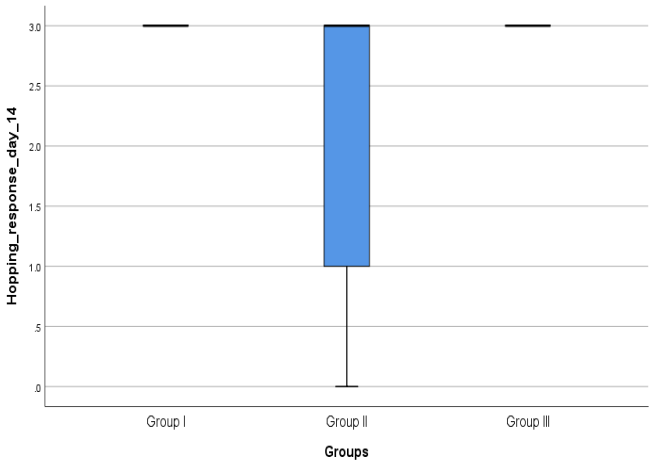

Figure 7. Box plot of between-group comparison of hopping response day 14

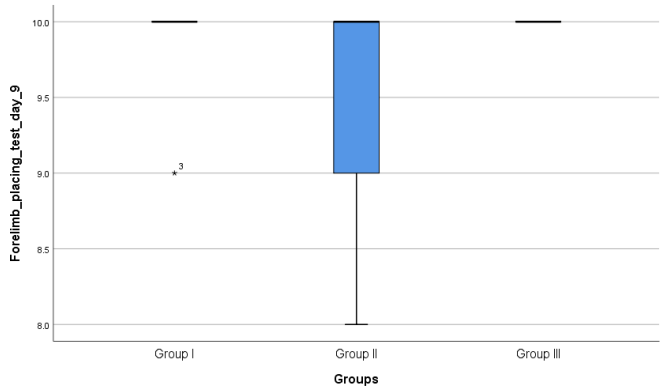

Figure 8. Box plot of between-group comparison of forward hand placement test day 9

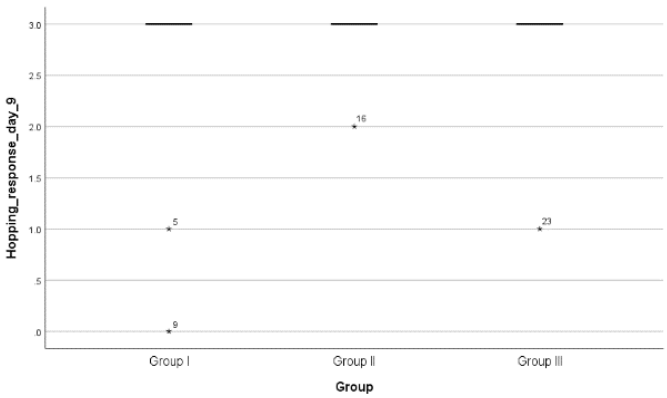

Figure 9. Box plot of between-group comparison of hopping response day 9

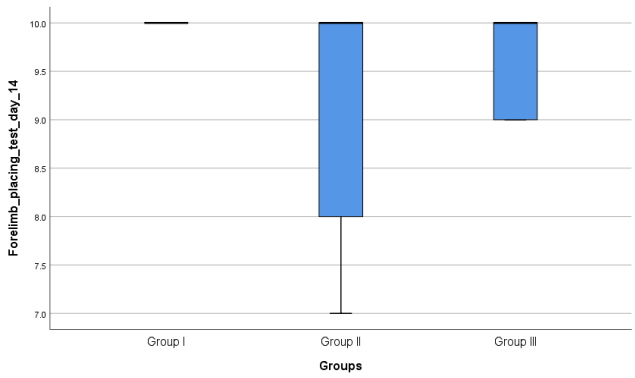

Figure 10. Box plot of between-group comparison of forward hand placement test day 14

there was no significant difference between groups in the hopping response on day 9 (Figure 9) (*p* = 0.78) and the forelimb placing test on day 14 (Figure 10) (*p* = 0.054). After adjustment for repeated comparison, all results were still significantly different except the hopping response on day 14 and the forelimb placing test on day 9.

B. Histological examination

The Pacinian (Figure 11) and Ruffini (Figure 12) corpuscles mechanoreceptors number: between groups comparisons (Table 2) showed a significant increase in the total number (Pacinian + Ruffini) (Figure 13) and Ruffini corpuscles number (Figure 14) in group I compared to group II (*p* = 0.003, 0.007,

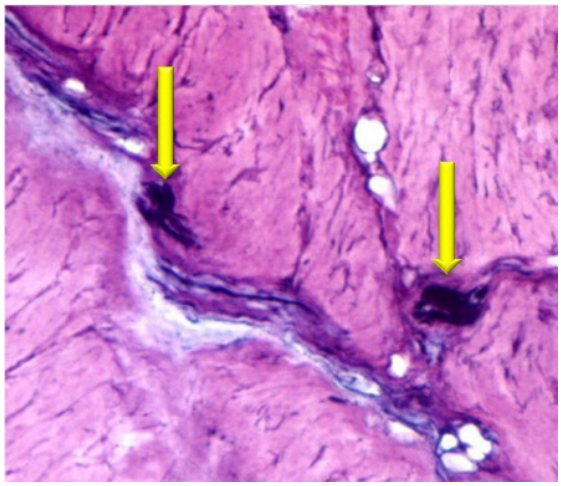

Figure 11. Pacinian corpuscles (400X) stained with modified gold chloride technique

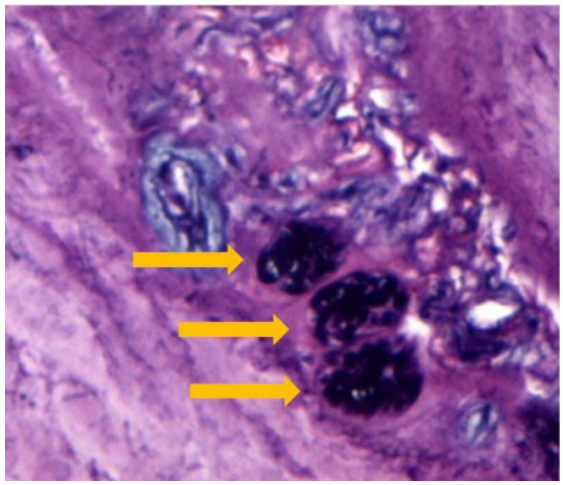

Figure 12. Ruffini corpuscles (400X) stained with modified gold chloride technique

respectively) with no significant difference compared to group III ($p = 0.18$, 0.23, respectively). However, there was no significant difference between groups in Pacinian corpuscle numbers ($p = 0.15$) (Figure 15).

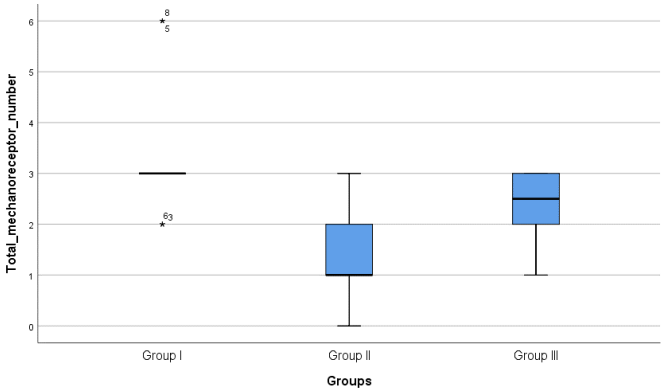

Figure 13. Box plot of between-groups comparison of the total number of mechanoreceptors

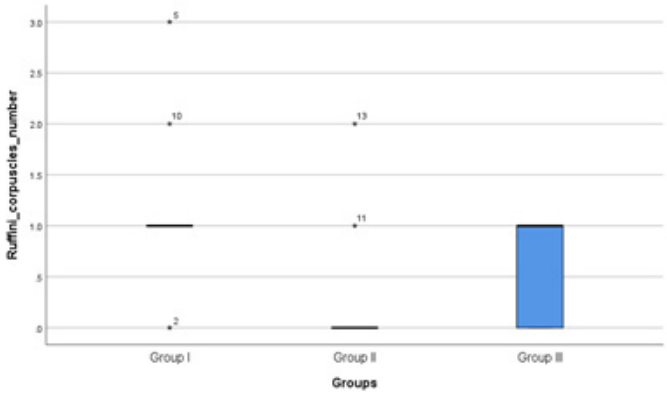

Figure 14. Box plot of between-group comparison of Ruffini corpuscles number

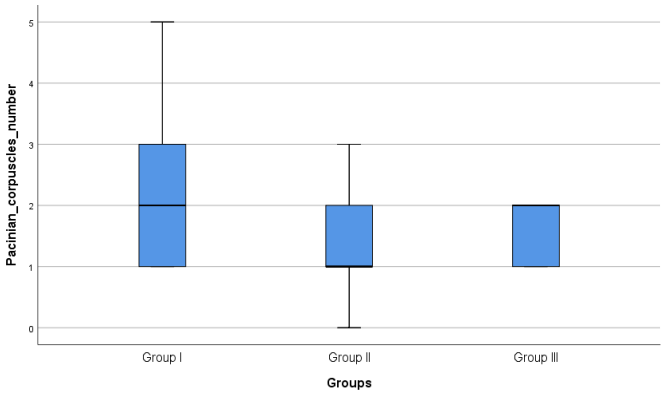

Figure 15. Box plot of between-group comparison of Pacinian corpuscles number

Table 2. Results of mechanoreceptor numbers presented as median (minimum–maximum)

Groups		Pacinian corpuscles number	Ruffini corpuscles number	Total mechanoreceptor number
Group I ($n = 10$)	median	2	1*	3**
	minimum	1	0	2
	maximum	5	3	6
Group II ($n = 9$)	median	1	0	1
	minimum	0	0	0
	maximum	3	2	3
Group III ($n = 8$)	median	2	1	2.5
	minimum	1	0	1
	maximum	2	1	3

* significantly increased relative to group II ($p = 0.003$)
** significantly increased relative to group II ($p = 0.007$)

Sciatic function index

Results of between-groups comparisons showed a non-significant difference (p = 0.7) (Table 3). Also, within-group comparisons showed a nonsignificant difference as follows: group I (p = 0.52), group II (p = 0.73), and group III (p > 0.99).

Table 3. Results of SFI analysis

Groups	SFI Median	Minimum	Maximum
Group I (n = 10)	–14.52	–21.63	12.97
Group II (n = 9)	–9.07	–28.05	1.86
Group III (n = 8)	–9.92	–15.10	7.43

Paw volume and body weight

Between-groups comparisons of paw volume (Table 4) showed a significant decrease on day 7 in group I compared to group II (p = 0.01) with no significant difference compared to group III (p = 0.54) (Figure 16). There was a significant increase in the day 7 and day 9 paw volume in group II compared to group III (p = 0.002, 0.01, respectively) with no significant difference between group I and group III (p = 0.54, 0.23, respectively) (Figures 16, 17).

Within-group analysis showed a significant increase in group II on day 7 relative to the previous examinations (days 2 and 4) (p = 0.007, 0.04, respectively) which persisted until the end of the study.

Table 5. Between-groups comparisons of body weight presented as median (minimum–maximum)

Groups		Weight day 0	Weight day 9	Weight pre-euthanasia
Group I (n = 10)	median	228.50*	223.50	224.00
	minimum	202	193	191
	maximum	246	239	246
Group II (n = 9)	median	197.00	215.00	203.00
	minimum	190	190	188
	maximum	229	235	233
Group III (n = 8)	median	216.50	220.50	213.50
	minimum	202	198	194
	maximum	242	266	251

* significant increase compared to group II (p = 0.009)

The between-groups comparisons of body weight (Table 5) showed a significant increase on day 0 in group I compared to group II (p = 0.009). However, it did not show a significant difference on day 9 (inflammatory onset) or in the pre-euthanasia assessment (p = 0.3, 0.32, respectively). Also, the within-group analysis did not show a significant difference between the start and end of the study: group I (p = 0.011) group II (p = 0.12), group III (p = 0.14).

Table 4. Between-group comparison of paw volume presented as median (minimum–maximum)

Groups		Paw volume day 2	Paw volume day 4	Paw volume day 7	Paw volume day 9	Paw volume day 11	Paw volume pre-euthanasia
Group I (n = 10)	median	9.5	11	10.5*	10	9.5	11
	minimum	8	8	8	8	8	9
	maximum	12	12	12	12	12	12
Group II (n = 9)	median	11	9	12**$	11***	9	11
	minimum	8	8	10	10	8	9
	maximum	12	11	13	13	12	12
Group III (n = 8)	median	9.5	9	10	10	9	10
	minimum	8.0	8.0	9.0	8.0	8.0	9.0
	maximum	12	11	11	11	10	11

* significant decrease compared to group II (p = 0.01)
** significant increase compared to group III (p = 0.002)
*** significant increase compared to group III (p = 0.01)
$ significant within-group increase relative to days 2 and 4 (p = 0.007, 0.04, respectively)

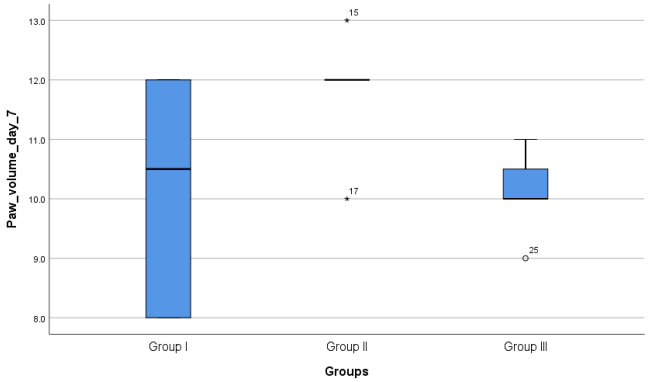

Figure 16. Box plot of between-group comparison of paw volume day 7

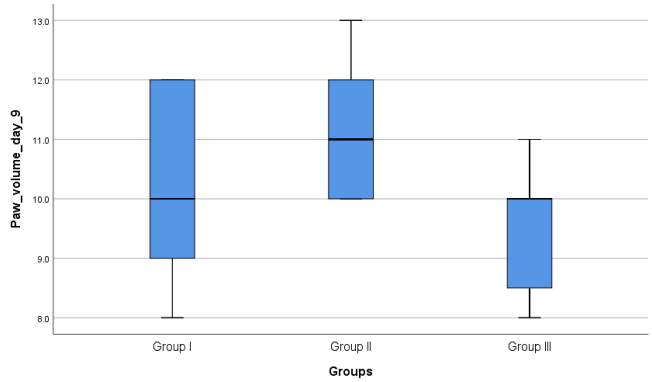

Figure 17. Box plot of between-group comparison of paw volume day 9

Discussion

The results show significant preservation of the number of proprioceptive receptors (Ruffini corpuscles) and functional testing in group I (treated RA model) relative to group II (untreated RA model / positive control) with no significant difference relative to group III (normal animals / negative control). Furthermore, there was a significant increase in paw volume (indicator of oedema) in group II on days 7 and 9 (onset of disease) without a significant difference between groups I and III. Regarding animal weight, there was a significant increase in group I relative to group II at the start of the study, then there was no significant difference between groups until the end of the study; however, the within-group analysis did not show any significant difference. Regarding the SFI, there was no significant difference between groups or within groups.

RA is a chronic autoimmune systemic disease that affects 1% of the population. Patients suffer from depletion of proprioceptors [27], which represents a significant proportion of the increased risk of falling and further injury, resulting in a fear of movement [28]. Recent RA research focuses on the remission phase (prophylactic) treatment, as it is proven to decrease arthritis severity and complications. However, this research is limited in humans for both ethical and clinical reasons, so animal models can offer a good alternative [29]. Animals can be selected to be homogenous in age, sex, genetics, and disease-modifying factors such as duration, severity, and lifestyle.

PEMF therapy has multiple positive effects on nerve regeneration and sprouting. For example, applying a PEMF (0.23 mT/50 Hz/96 h) to a rat pheochromocytoma culture increases the average number of neurites per cell to 2.4 compared to 1.9 in control cells [30]. Furthermore, a PEMF (1.36 mT/50Hz/ 96 h) increases the average length of neurites [31]average length of neurites, and directivity of neurite outgrowth in PC12 cells cultured for 96 h in the presence of nerve growth factor (NGF. This increase could be attributed to the up-regulation of neurotrophic factor gene expression and increased resistance to oxidative stress [32]at least in part, to the effect of these fields on neurotrophic factors levels and cell survival, leading to an improvement in behavior. This study was undertaken to investigate the neuroprotective effects of ELFEF in a rat model of 3-nitropropionic acid (3NP. Furthermore, it can increase the number of mechanoreceptors in healthy rats [33], upregulate the expression of the mRNA transcription factors that direct the differentiation of new cells into neuronal cells rather than the glial phenotype, increase the levels of mRNA for Ca^{+2} channel subunits that mediate neurogenesis [34], and inhibit H2O2-induced apoptosis and puromycin production, which is a protein synthesis inhibitor that stops DNA ribosome translation [35]. Moreover, magnetic therapy has been proven to decrease pain [36] and inflammation [11] in RA patients, which can indirectly improve proprioception and balance.

To the best of the authors' knowledge, there are no randomised controlled trials on the effect of a PEMF on proprioception receptors or function in RA patients or models. Therefore, this study aimed to investigate the effect of a PEMF primarily on proprioception in terms of the number and function of mechanoreceptors and secondarily on gait quality (sciatic function index) and arthritis severity in an AIA model of RA. The results show a significant preservation of the number of mechanoreceptors (Ruffini corpuscles) and proprioceptive function in group I (treated RA model) relative to group II (untreated RA model) without a significant difference relative to group III (normal animals). Furthermore, there was a significant increase in paw volume (indicator of oedema) in group II on days 7 and 9 (onset of disease) without a significant difference between groups I and III, which agrees with previous studies [11, 37]. For animal weight, there was a significant increase in group I relative to group II at the start of the study, followed by no significant difference between groups until the end of the study; however, the within-group analysis did not show any significant difference. For the SFI, there was no significant difference between groups. Based on these findings, PEMF treatment has a positive effect on the number and function of the proprioceptors in the AIA model tested and may have a role in balance preservation and falling risk reduction in humans.

Previous studies also support the application of a PEMF for RA treatment, as it enhances stem cells differentiation, joint regeneration and vascular homeostasis [38], decreases pain and inflammation, regulates the immune system, and enhances tissues survival by maintaining redox homeostasis [36], and decreases standing body sway during transcranial PEMF exposure [39] without any side effects.

The insignificant differences in the SFI could be attributed to the different morphology between bipedal humans and quadrupedal rat mechanics. Also, insignificant changes in body weight may be a result of a minimal amount or lack of pain, which was intended to not affect appetite, as this study was carried out during the remission phase.

This study has a few limitations. First, we investigated the effect of PEMF with specific parameters in the remission phase of an AIA model, so further studies can investigate the effect of different parameters and different therapeutic techniques, such as microcurrent [40]pain threshold, range of motion, neck muscle strength, and neck function. Methods. It is a pilot study involving 28 female subjects (aged 18 24 years, in different RA phases. Also, the examination was carried out at the end of the remission phase; However, a longer follow-up may reveal an effect on the severity or progression of pathological changes in advanced RA stages. Furthermore, only histological and functional analyses were performed as endpoint assessments, whereas biomechanical and other neurophysiological studies can also be considered. Moreover, the histology was based on manual counting, so further studies can use an image analyser or histomorphometry, or electron microscopy to gain a better insight into the neural changes and to decrease the subjectivity of this process. Also, different balance mechanisms can make balance defects less clinically presented in quadrupeds; So, if the validity of the AIA model is assumed in the bipedal model, it will be more suitable for similar studies. Finally, the sample size was based on recommendations for this type of research and no sample size calculation was performed, which may result in low statistical power. Therefore, further studies should consider sample size calculation based on the current results to decrease type II statistical error.

Conclusions

Within the limitations of this study, PEMF treatment for 1 hour, 6 days/week for 2 weeks can effectively preserve proprioception functionally and structurally and decrease oedema in a rodent animal model of RA.

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Conflict of interest

The authors state no conflict of interest.

Disclosure statement

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References

1. Wiegmann S, Armbrecht G, Borucki D, Buehring B, Buttgereit F, Detzer C et al. Association between sarcopenia, physical performance and falls in patients with rheumatoid arthritis: a 1-year prospective study. BMC Musculoskelet Disord. 2021;22:885; doi: 10.1186/s12891-021-04605-x.
2. Jin S, Hsieh E, Peng L, Yu C, Wang Y, Wu C et al. Incidence of fractures among patients with rheumatoid arthritis: a systematic review and meta-analysis. Osteoporos Int. 2018;29(6):1263–1275; doi: 10.1007/s00198-018-4473-1.
3. Armstrong C, Swarbrick CM, Pye SR, O'Neill TW. Occurrence and risk factors for falls in rheumatoid arthritis. Ann Rheum Dis. 2005;64:1602–1604; doi: 10.1136/ard.2004.031195.
4. Aydog E, Bal A, Aydog ST, Çakci A. Evaluation of dynamic postural balance using the Biodex Stability System in rheumatoid arthritis patients. Clin Rheumatol. 2006;25:462–467; doi: 10.1007/s10067-005-0074-4.
5. Agarwal V, Singh R, Wiclaf, Chauhan S, Tahlan A, Ahuja CK et al. A clinical, electrophysiological, and pathological study of neuropathy in rheumatoid arthritis. Clin Rheumatol. 2008;27:841–844; doi: 10.1007/s10067-007-0804-x.
6. Böhler C, Radner H, Ernst M, Binder A, Stamm T, Aletaha D et al. Rheumatoid arthritis and falls: the influence of disease activity. Rheumatol. 2012;51(11):2051–2057; doi: 10.1093/rheumatology/kes198.
7. Williams SB, Brand CA, Hill KD, Hunt SB, Moran H. Feasibility and outcomes of a home-based exercise program on improving balance and gait stability in women with lower-limb osteoarthritis or rheumatoid arthritis: a pilot study. Arch Phys Med Rehabil. 2010;91(1):106–114; doi: 10.1016/j.apmr.2009.08.150.
8. Neuberger GB, Aaronson LS, Gajewski B, Embretson SE, Cagle PE, Loudon JK et al. Predictors of exercise and effects of exercise on symptoms, function, aerobic fitness, and disease outcomes of rheumatoid arthritis. Arthritis Care Res. 2007;57:943–952; doi: 10.1002/art.22903.
9. Gibson W, Arendt-Nielsen L, Taguchi T, Mizumura K, Graven-Nielsen T. Increased pain from muscle fascia following eccentric exercise: animal and human findings. Exp Brain Res. 2009;194:299–308; doi: 10.1007/s00221-008-1699-8.
10. Efthimiou P, Kukar M. Complementary and alternative medicine use in rheumatoid arthritis: Proposed mechanism of action and efficacy of commonly used modalities. Rheumatol Int. 2010;30:571–586; doi: 10.1007/s00296-009-1206-y.
11. Kumar VS, Kumar DA, Kalaivani K, Gangadharan AC, Raju KVSN, Thejomoorthy P et al. Optimization of pulsed electromagnetic field therapy for management of arthritis in rats. Bioelectromagnetics. 2005;26(6):431–439; doi: 10.1002/bem.20100.
12. Bendele A. Animal models of rheumatoid arthritis. J Musculoskelet Neuronal Interact. 2001;1(4):377–85.
13. Trentham DE, Townes AS, Kang AH. Autoimmunity to type II collagen an experimental model of arthritis. J Exp Med. 1977;146(3):857–868; doi: 10.1084/jem.146.3.857.
14. Tominaga K, Alstergren P, Kurita H, Kopp S. Clinical course of an antigen-induced arthritis model in the rabbit temporomandibular joint. Oral Pathol Med. 1999;28(6):268–273; doi: 10.1111/j.1600-0714.1999.tb02037.x.
15. Tesarz J, Hoheisel U, Wiedenhöfer B, Mense S. Sensory innervation of the thoracolumbar fascia in rats and humans. Neuroscience. 2011;194:302–8; doi: 10.1016/j.neuroscience.2011.07.066.
16. Willard FH, Vleeming A, Schuenke MD, Danneels L, Schleip R. The thoracolumbar fascia: anatomy, function and clinical considerations. J Anat. 2012;221(6):507–536; doi: 10.1111/j.1469-7580.2012.01511.x.
17. Chaudhry H, Max R, Antonio S, Findley T. Mathematical model of fiber orientation in anisotropic fascia layers at large displacements. J Bodyw Mov Ther. 2012;16(2):158–164; doi: 10.1016/j.jbmt.2011.04.006.
18. An YH, Freidman RJ (eds). Animal models in orthopaedic research. Boca Raton: CRC Press; 2020; doi: 10.1201/9780429173479.
19. Hukkanen M, Gronblad M, Rees R, Konttinen YT, Gibson SJ, Hietanen J et al. Regional distribution of mast cells and peptide containing nerves in normal and adjuvant arthritic rat synovium. Rheumatol. 1991;18(2):177–183.
20. Bendele A, McComb J, Gould T, McAbee T, Sennello G, Chlipala E et al. Animal models of arthritis: relevance to human disease. Toxicol Pathol. 1999;27(1):134–142; doi: 10.1177/019262339902700125.
21. Thalhammer JG, Vladimirova M, Bershadsky B, Strichartz GR. Neurologic evaluation of the rat during sciatic nerve block with lidocaine. Anesthesiology. 1995;82(4):1013–1025; doi: 10.1097/00000542-199504000-00026.
22. Krafft PR, McBride DW, Lekic T, Rolland WB, Mansell CE, Ma Q et al. Correlation between subacute sensorimotor deficits and brain edema in two mouse models of intracerebral hemorrhage. Behav Brain Res. 2015;264:151–160; doi: 10.1016/j.bbr.2014.01.052.
23. Koch B, Kurriger G, Brand RA. Characterisation of the neurosensory elements of the feline cranial cruciate ligament. J Anat. 1995;187(Pt 2):353–359.
24. Wageh H, Mohammad T, Elias MM, Elwafa NA, Nabhan M, Hassan NS et al. Standardizing sciatic function index rating protocol improves inter-rater reliability and precision of novice assessors. 20th International Scientific Conference Faculty of Physical Therapy Cairo. 2019.
25. Parkkinen S, Ortega FJ, Kuptsova K, Huttunen J, Tarkka I, Jolkkonen J. Gait impairment in a rat model of focal cerebral ischemia. Stroke Res Treat. 2013;410972; doi: 10.1155/2013/410972.
26. Fereidoni M, Ahmadiani A, Semnanian S, Javan M. An accurate and simple method for measurement of paw edema. J Pharmacol Toxicol Methods. 2000;43(1):11–14; doi: 10.1016/s1056-8719(00)00089-7.
27. Miller LE, Jüsten HP, Schölmerich J, Straub RH. The loss of sympathetic nerve fibers in the synovial tissue of patients with rheumatoid arthritis is accompanied by increased norepinephrine release from synovial macrophages. FASEB J. 2000;14(13):2097–2107; doi: 10.1096/fj.99-1082com.
28. Metlı NB, Kurtaran A, Akyüz M. Impaired balance and fall risk in rheumatoid arthritis patients. Turk J Phys Med Rehab. 2015;61:344–351; doi: 10.5152/tftrd.2015.69379.

29. Dekkers JS, Schoones JW, Huizinga TW, Toes RE, van der Helm-van Mil AH. Possibilities for preventive treatment in rheumatoid arthritis? Lessons from experimental animal models of arthritis: a systematic literature review and meta-analysis. Ann Rheum Dis. 2017;76:458–467; doi: 10.1136/annrheumdis-2016-209830.
30. Fan W, Ding J, Duan W, Zhu YM. The influence of magnetic fields exposure on neurite outgrowth in PC12 rat pheochromocytoma cells. J Magn Magn Mater. 2004;282: 325–328; doi: 10.1016/j.jmmm.2004.04.076.
31. Zhang Y, Ding J, Duan W, Fan W. Influence of pulsed electromagnetic field with different pulse duty cycles on neurite outgrowth in PC12 rat pheochromocytoma cells. Bioelectromagnetics. 2005;26(5):406–411; doi: 10.1002/bem.20116.
32. Tasset I, Medina FJ, Jimena I, Agüera E, Gascón F, Feijóo M et al. Neuroprotective effects of extremely low-frequency electromagnetic fields on a Huntington's disease rat model: effects on neurotrophic factors and neuronal density. Neuroscience. 2012;209:54–63; doi: 10.1016/j.neuroscience.2012.02.034.
33. Nabhan MMM, Mohammed HSE-D, Balbaa AEAE. Effect of electromagnetic therapy on mechanoreceptor number as a risk factor of low back pain. 17th International Scientific Conference Faculty of Physical Therapy Cairo. 2016.
34. Cuccurazzu B, Leone L, Podda MV, Piacentini R, Riccardi E, Ripoli C et al. Exposure to extremely low-frequency (50 Hz) electromagnetic fields enhances adult hippocampal neurogenesis in C57BL/6 mice. Exp Neurol. 2010; 226(1):173–182; doi: 10.1016/j.expneurol.2010.08.022.
35. Grassi C, D'Ascenzo M, Torsello A, Martinotti G, Wolf F, Cittadini A et al. Effects of 50 Hz electromagnetic fields on voltage-gated Ca2+ channels and their role in modulation of neuroendocrine cell proliferation and death. Cell Calcium. 2004;35(4):307–315; doi: 10.1016/j.ceca.2003.09.001.
36. Gajewski M, Rzodkiewicz P, Maśliński S, Wojtecka-Łukasik E. The role of physiological elements in future therapies of rheumatoid arthritis. III. The role of the electromagnetic field in regulation of redox potential and life cycle of inflammatory cells. Reumatologia. 2015;53(4): 219–224; doi: 10.5114/reum.2015.54000.
37. Selvam R, Ganesan K, Narayana Raju KVS, Gangadharan AC, Manohar BM, Puvanakrishnan R. Low frequency and low intensity pulsed electromagnetic field exerts its antiinflammatory effect through restoration of plasma membrane calcium ATPase activity. Life Sci. 2007; 80(26):2403–2410; doi: 10.1016/j.lfs.2007.03.019.
38. Ross CL, Ang DC, Almeida-Porada G. Targeting mesenchymal stromal cells/pericytes (MSCs) with pulsed electromagnetic field (PEMF) has the potential to treat rheumatoid arthritis. Front Immunol. 2019;10:266; doi: 10.3389/fimmu.2019.00266.
39. Thomas AW, White KP, Drost DJ, Cook CM, Prato FS. A comparison of rheumatoid arthritis and fibromyalgia patients and healthy controls exposed to a pulsed (200 microT) magnetic field: effects on normal standing balance. Neurosci Lett. 2001;309(1):17–20; doi: 10.1016/s0304-3940(01)02009-2.
40. Battecha KH, Kamel DM, Tantawy SA. Investigating the effectiveness of adding microcurrent therapy to a traditional treatment program in myofascial pain syndrome in terms of neck pain and function. Physiother Quart. 2021;29(1):17–23; doi: 10.5114/pq.2020.96421.