The impact of eccentric muscle contractions on peripheral nerve integrity

Article *in* European Journal of Applied Physiology · December 2024

DOI: 10.1007/s00421-024-05668-z

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INVITED REVIEW

The impact of eccentric muscle contractions on peripheral nerve integrity

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Received: 16 June 2024 / Accepted: 16 November 2024

Abstract

Background and aims Besides muscle damage, eccentric contractions also impose significant mechanical loads on peripheral nerves. However, the impact of eccentric contractions on peripheral nerve properties remains unclear. We aimed to reveal the immediate (i.e., <2 h and short-term (i.e., <10 days) effects of eccentric contractions on functional, structural, morphological, physiological and biomechanical properties of peripheral nerves.

Methods Four electronic databases (PubMed, Science Direct, PEDro and Cochrane) were searched for animal and human studies which evaluated the immediate and/or short-term impact of eccentric contractions of upper or lower limb muscles on outcomes related functional, structural, morphological, physiological and biomechanical properties of peripheral nerves.

Results From a total of 2415 articles, two human and two animal studies met the selection criteria. Several signs of nerve damage following eccentric exercises were observed, such as reductions in myelin sheath thickness, nerve fibre diameter, sensory and motor nerve conduction velocity, and protein zero levels, alongside increased levels of macrophage-related protein and tropomyosin receptor kinase C. No significant changes were identified in growth-associated protein 43. It is worth noting that some variables exhibited differences in their time course between human and animal studies. Animal studies revealed that the effects were more pronounced when eccentric contractions were performed at higher velocities.

Conclusion Current evidence is suggestive that eccentric contractions has the potential to alter the peripheral nerves structural, morphological, functional and physiological properties, which are indicative of nerve damage.

Systematic Review Registration: CRD42021285767

Keywords Eccentric · Nerve damage · Mononeuropathy · Peripheral nerves · Mononeuropathy · SYstematic Review Centre for Laboratory animal · Experimentation (SYRCLE)'s Risk of Bias (RoB) tool · SYstematic Review Centre for Laboratory animal · Experimentation (SYRCLE)'s Risk of Bias (RoB) tool

Introduction

Skeletal muscle eccentric contractions involve the active lengthening of the muscle-tendon unit under tension (Lieber 2018; Lindstedt et al. 2001). It is well documented that eccentric rather than concentric or isometric

Communicated by Michael I Lindinger.

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Published online: 04 December 2024

contractions are known to induce muscle damage due to excess tension during contractions (Lavender and Nosaka 2006). High levels of this type of contraction are likely to produce muscle soreness and muscle damage that peak between 24–72 h post-exercise and disappear within 5–7 days (Nosaka et al. 2002). The magnitude of these effects is greater in untrained people (Newton et al. 2008), and when contractions are performed at longer muscle lengths (Sadacharan and Seo 2021), higher loads (Merrigan and Jones 2021), and faster contraction velocities (Chapman et al. 2006). The resulting muscular inflammatory response can spread through the extracellular matrix and connective tissue components (Stauber et al. 1990). This is plausible to cause further damage to non-muscular tissues, such as peripheral nerves. For instance, sciatic nerve damage was observed after gastrocnemius muscle contusion (Kami et al. 1999). Consequent regenerative reactions have been found at both levels, in intramuscular nerves and in spinal motoneurons, such as upregulation of glial cell line-derived neurotrophic factor and the corresponding receptor GFR-α1 mRNAs in Schwann cell-like cells (Kami et al. 1999). Also, decreased nerve conduction velocity (NCV) of the sciatic nerve was observed in the injured limb of athletes who had experienced hamstring muscle strain injuries, compared to the uninjured side (Kouzaki et al. 2017). These findings suggest that the nerve inflammatory process likely occurs near the injured muscle, and then might spread toward the spinal cord.

Peripheral nerves are also known to experience mechanical loads during limb movement (Bueno and Shah 2008), including during eccentric contractions. Depending on limb positioning, peripheral nerves are mechanically subjected to strain, compressive, torsion and shear forces. When excessive, these forces can lead to tissue damage (Kouzaki et al. 2016, Lee et al. 2014). It should be noted that under optimal amounts of tensile loading, nerve growth may be facilitated or even accelerated (Ellis et al., 2022); Love et al. 2017). For instance, with nerve strain Schwann cells promote myelin synthesis, demonstrated by increased levels of myelin basic protein (Love et al. 2017) and protein zero (Hara et al. 2003). However, excessive tensile strains lead to structural and functional deficits to the nerve (Singh et al. 2009). Previous animal and human studies have attempted to find the physiological limit of nerve elongation before injury, but have failed to agree on an absolute strain limit value (Liu et al. 1948; Wall et al. 1992; Brown et al. 1993). Other variables such as the nerve elongation rate (Haftek 1970; Singh et al. 2009), the strain duration (Fowler et al. 2001), and strain frequency (Barberio et al. 2019) are also thought to play a role on the magnitude of nerve damage. Besides, compression strain may also be created by increased pressure in the extraneural environment or due to increased longitudinal strain (Grewal et al. 1996). Consequently, injury to the perineurium (Lundborg and Rydevik 1973) and epineurium (Haftek 1970) may occur, thus leading to endoneurial edema (Lundborg 1970; Lundborg et al. 1983). However, although some studies acknowledge that eccentric contractions may induce changes in peripheral nerve properties, the notion that these alterations reflect damage to peripheral nerves is not commonly addressed in the literature.

This study aimed to systematically search the literature and synthetize current evidence on the immediate (i.e., <2 h) and short-term (i.e., <10 days) effects of eccentric muscle contractions on peripheral nerve functional, structural, morphological, physiological and biomechanical properties, from both animal and human studies. In addition, based on the studies found, we aimed to identify some future areas of research on this topic. In order to be able to attribute pathological findings to eccentric contractions, and not to pre-existing nerve pathology, only findings in healthy individuals and animals without pre-existing muscle or nerve pathology were considered.

Methods

This study was registered on the International Prospective Register of Systematic Reviews (PROSPERO, on 17 November 2021, Registration number: CRD42021285767) and is compliant with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Page et al. 2021). The protocol of this study has been previously published (Lungu et al. 2023).

Search strategy

A systematic search of the literature was conducted in Medline/PubMed, Science Direct, PEDro and Cochrane from database inception to 30th August 2023. The search was conducted without date and methodological quality restrictions. The syntaxes used for the search included keywords and synonyms relating to eccentric contractions, and nerve function, structure, morphology, physiology and biomechanics which are detailed in the online supplemental material (Appendix 1).

Study selection

The study selection was performed by two independent reviewers (DL and TN). After removing duplicate records, titles and abstracts were initially screened based on predetermined selection criteria. The full text of potentially relevant studies was retrieved and screened for eligibility. Studies

that fulfilled the selection criteria were included after all the authors approval. Conflicts at either stage were resolved by consensus moderation.

Study eligibility criteria

A summary of the selection criteria for participants, interventions, comparators, and outcomes (PICO strategy), as well as the type of studies is shown in Table 1.

Methodological quality assessment

Two independent reviewers (DL and TN) assessed the risk of bias of eligible trials. Animal studies were evaluated using the Risk of Bias (RoB) tool for animal intervention studies–Systematic Review Centre for Laboratory animal Experimentation (SYRCLE)'s RoB tool, based on the original Cochrane RoB Tool. This tool is recommended to assess the methodological quality of animal intervention studies (Ma et al. 2020). SYRCLE's RoB tool contains 10 items related to 6 types of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases. In order to assign a judgment of low, high or unclear risk of bias to each item of the tool, a detailed list with signalling questions is proposed to aid the judgment process. A "yes" score indicates low risk of bias, while "no" indicates high risk of bias; the score is "unclear" if insufficient details have been reported to assess the risk of bias properly (Hooijmans et al. 2014). To evaluate non-randomised interventional studies, the Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) was used (Sterne et al. 2016). This tool is guided through seven chronologically arranged bias domains (pre-intervention, at intervention, and post-intervention), and the interpretations of domain-level and overall risk of bias judgement in ROBINS-I are classified in low, moderate, serious, or critical risk of bias (Sterne et al. 2016). Differences between both reviewers were resolved by a consensus meeting. The inclusion of a third reviewer was not required.

Table 1 Overview of the selection criteria according to PICO strategy and type of studies

Selection criteria according to PICO strategy and type of studies
Population (paragraph) Inclusion criteria
–Animal studies, involving healthy adult animals, considering all species, sex and weight.
–Human studies, involving healthy asymptomatic adults (i.e., >18 years), considering both sexes, race, ethnicity or other demographic characteristics.
Exclusion criteria
– Articles that evaluated changes with age comparing the effects of eccentric contractions between young and elderly animals or subjects were excluded.
Intervention
– Eccentric contractions of upper or lower limb skeletal muscles.
Comparison
– No intervention; i.e., no other modality or a different protocols of eccentric contractions (i.e., different number of series and sets, angular velocities, multiple bouts).
Outcomes
Function: Sensory and motor nerve function–nerve conduction velocity.
Structure and morphology (from micro to macro levels): nerve fibre diameter and myelin sheath thickness (via microscopic analysis); fascicle number (i.e., axon density) and size (i.e., diameter) by high frequency ultrasonography or magnetic resonance microscopy; nerve thickness by ultrasound (US) or magnetic resonance imaging (MRI) or microscopic analysis; nerve cross sectional area (CSA) by US or MRI or microscopic analysis; nerve volume with freehand 3D US or MRI.
Physiology: intraneural blood flow measured with Doppler US (B-mode with Colour Doppler) or laser doppler flowmetry; change in molecular expressions (proteins): myelin sheath protein zero (p0); growth-associated protein 43 (GAP-43); myelin-associated glycoprotein (MAG); peripheral myelin protein 22 (PMP22); galectin-3/MAC-2; tropomyosin receptor kinase C (TrkC); neurotrophins [nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3) and neurotrophin 4/5 (NT-4/5)] (through immunohistochemistry); serum levels of neuroinflammatory mediators (or through immunohistochemistry), such as cytokines, neuropeptides, reactive oxygen species, and chemokines; alterations in signal intensity (T1 and T2 via MRI) and echo intensity (via high-resolution US). Biomechanics: nerve strain; excursion, and stiffness via US and US elastography (shear wave elastography).
Type of studies
Included
– Randomised controlled trial and non-randomised controlled trials (quasi-experimental studies).
– Published in English, peer-reviewed and available in full-text.
Excluded
– Reviews, case reports, editorials, protocol studies, clinical guidelines, and conference articles.

Data extraction

Data extraction was performed by two authors independently of each other (DL and TN). Study characteristics extracted were: (1) identification of the study (i.e., authors and publication year); (2) methodological characteristics (i.e., sample characteristics (sample size; sex; age; human/animals); groups and controls: characteristics of eccentric contractions (e.g., number of repetitions; number of series; angular velocity; number of sessions, duration, and muscle (group) targeted); type of control condition; outcomes measured (e.g., change in nerve function, structure, morphology, physiology and biomechanical properties); stated length of follow-up (after intervention)); (3) main findings.

Data analysis

A meta-analysis of the studies could not be performed due to the low number of identified studies and heterogeneity of their characteristics. However, a narrative synthesis was conducted for all included studies and variables.

Results

The literature search identified 2415 articles. After removing duplicates (n = 452) and following exclusion based on title and abstract screening (n = 1963), 59 reports were considered as potentially relevant. In the full-text analysis, 55 studies were excluded, mainly because they did not report any outcome of interest. In total, two animal studies (Lee et al. 2014; Kouzaki et al. 2016) and two human studies (Ochi et al. 2020; Ochi et al. 2021) were included in the systematic analysis. Fig. 1 illustrates the PRISMA flow diagram.

Methodological quality

In animal studies, results differed regarding selection bias. Random housing, selective outcome reporting and other sources of bias were classified as low risk of bias. For the remaining items, unclear risk of bias was observed. Human studies revealed an overall low (Ochi et al. 2020) and moderate (Ochi et al. 2021) methodological quality. Regarding Ochi et al., (2021) although most domains were considered low risk, the risk of bias overall was considered to be moderate due to potential bias in the selection of the reported result domain. Figs. 2 and 3 present the results of the methodological quality assessment of animal and human studies, respectively.

Characteristics of the studies

The main characteristics of the included animal and human studies are presented in Table 2. Overall, the sample comprised a total number of 120 male Wistar rats (mean age: 10 weeks (range 9–11 weeks)) and 44 untrained young adult humans (all male) (mean (SD) age: 19.7 (1.0) years).

With respect to the applied stimuli, three studies applied a single bout of eccentric contractions (Lee et al. 2014; Ochi et al. 2020; Ochi et al. 2021). A fourth study implemented the same protocol of eccentric contractions as Lee et al., (2014) and applied a single bout of eccentric contraction every 2 days, over 7 days, attaining a total of 4 bouts (Kouzaki et al. 2016).

In the animal studies, rats were divided in three groups: a group of slow velocity eccentric contraction (i.e., 30°/s), a group of fast velocity contraction (i.e., 180°/s) and a control group that did not receive any intervention. Eccentric contractions were induced by electrical stimulation of the gastrocnemius muscle with simultaneous forced dorsiflexion of the ankle joint, from 0º to 45º. In both human studies, a single velocity of 60°/s was used. One upper limb performed the eccentric contractions while the non-exercised contralateral arm served as control (no intervention).

Immediate effects (i.e., <2 h–ours after the eccentric contractions) were assessed only in human studies. Short-term effects (i.e., <10 days) were evaluated differently among studies, ranging between 1 to 10 days after the eccentric exercise regimen. The animal studies targeted the sciatic nerve, and the human studies the median nerve.

Effects on nerve function

All included studies evaluated conduction velocity and the main results are summarised in Fig. 4. Both animal studies reported a decrease in sciatic motor NCV following fast eccentric contractions (180º/s), but not with slow eccentric contractions (30º/s) (Lee et al. 2014; Kouzaki et al. 2016). Lee et al., (2014) observed a 21% decrease in motor NCV at day 7, after a single bout of eccentric contractions. However, after 2 and 4 bouts, decreases ranged from 22% to 58% between the 4th and 8th day following the stimuli, respectively.

Both human studies reported a decline in motor NCV immediately after exercise, with a 21.8% reduction in NCV when compared to before eccentric exercises. A decrease was observed on Day 1 (i.e., 17.4%) and Day 2 (i.e., 15.1%), with progressive increase over the days up to Day 5 (Ochi et al. 2020; Ochi et al. 2021). Regarding sensory NCV, a 16.2% decrease was noted immediately after eccentric contractions (Ochi et al. 2021). The highest reduction was observed one day after exercise (i.e., 41.6%), and then

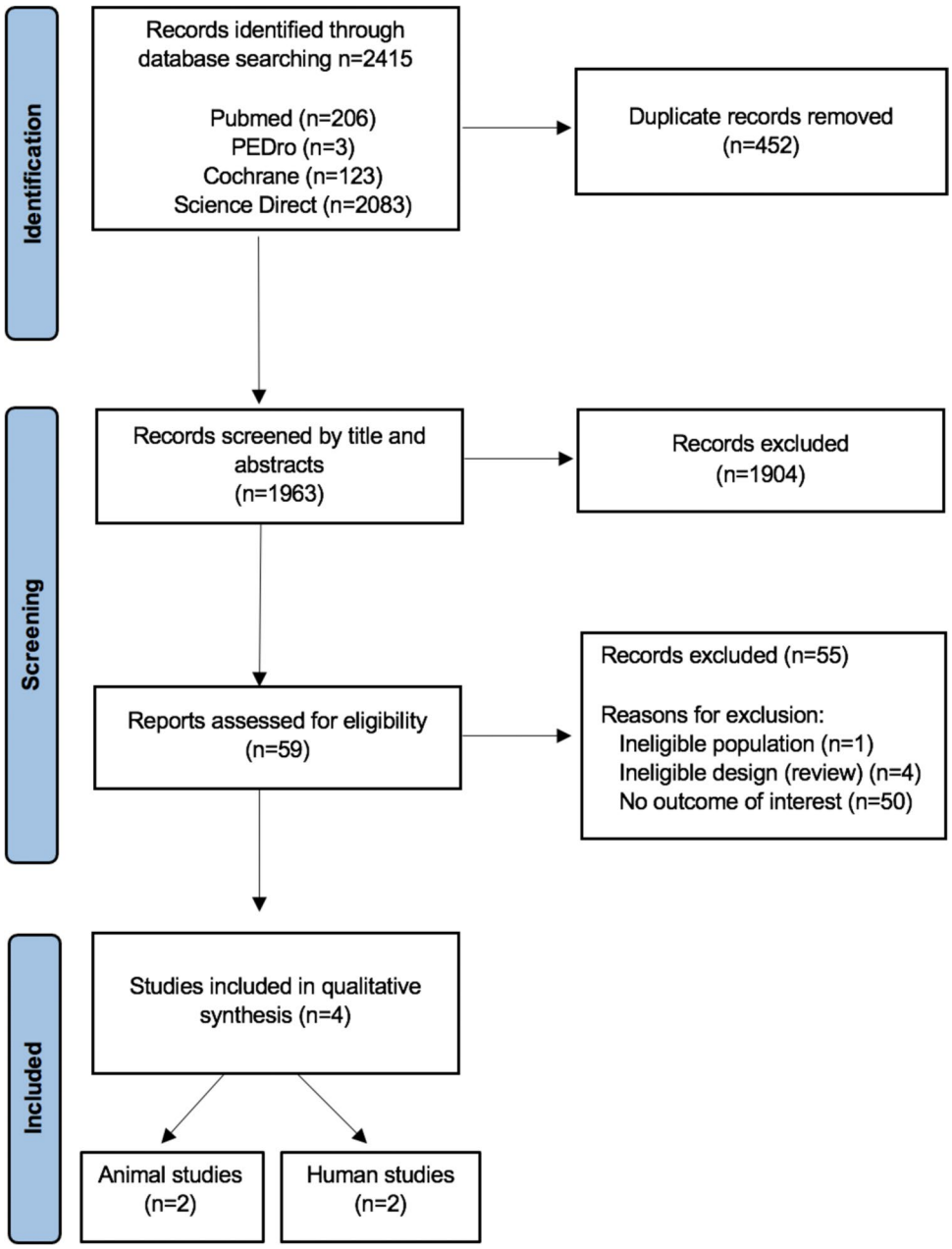

Fig. 1 The PRISMA flow diagram illustrating the study selection process

improved progressively over the days until Day 5 (i.e., Day 2: 37.57%; Day 3: 24.8%; Day 5: 10.9%) (Ochi et al. 2021).

Effects on nerve structure and morphology

One animal study assessed the effects of eccentric contractions on nerve structure and morphology one day after four bouts of eccentric contractions (i.e., on Day 8) (Kouzaki et al. 2016). Decreased myelin sheath thickness and sciatic nerve fibre diameter were found in the group that performed eccentric contractions at fast (180°/s) angular velocity. No significant alterations were observed in the slow (30°/s) angular velocity group. The myelin sheath thickness decreased by 20.6% and the nerve fibre diameter by 11.2% in the fast velocity group compared to the control group.

Effects on nerve physiology

One animal study (Lee et al. 2014) used immunohistochemistry to evaluate the impact of eccentric contractions on the levels of protein concentration, such as p0, ED1, TrkC and GAP-43. Effects were noted in the group that performed the fast eccentric contractions, with negligible changes in the slow velocity group. In the fast velocity group, on Day 3 after the eccentric contractions, no difference was observed in the levels of p0, ED1 and TrkC. However, on Day 7, p0

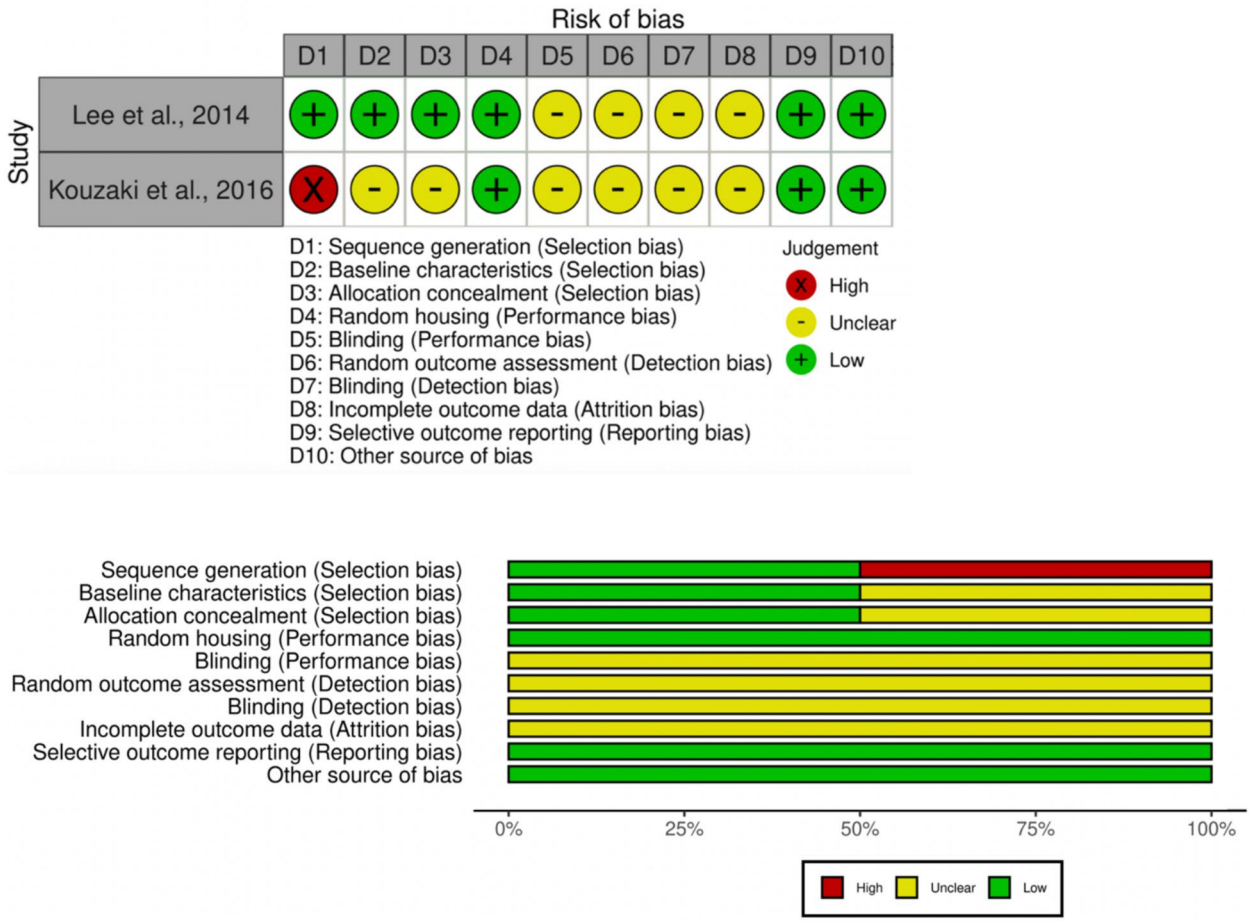

Fig. 2 Methodological quality of the animal studies using SYRCLE's risk of bias tool

decreased, and ED1 and TrkC increased. On day 10, p0 increased and ED1 and TrkC levels decreased. No significant alterations were identified in GAP-43 across the days.

Effects on nerve biomechanics

No study investigated the effects of eccentric contractions on peripheral nerve biomechanical properties (e.g., nerve excursion, strain and stiffness).

The main findings regarding the effects of eccentric muscle contraction on peripheral nerve properties are summarised in Fig. 5.

Discussion

Overall, findings of this systematic review revealed that eccentric contractions result in immediate and short-term alterations in peripheral nerve function (i.e., reduced motor and sensory NCV), structure and morphology (i.e., decreased myelin sheath thickness and fibre diameter), and physiology (i.e., lower levels of p0; increase in ED1 and TrkC concentration). In addition, findings from animal studies showed that changes are more pronounced when eccentric contractions were performed at fast angular velocity. No studies investigated biomechanical changes.

Effects of eccentric contractions on nerve function

Our results showed reduced nerve function, by a decline in motor (Lee et al. 2014; Kouzaki et al. 2016; Ochi et al. 2020) and sensory (Ochi et al. 2021) NCV, following eccentric contractions across all the included studies. However, some differences between animal and human studies regarding immediate and short-term effects were noted. Human studies revealed decreased motor NCV immediately after eccentric contractions, while sensory NCV reached the lowest value on Day 1. Both, sensory and motor NCV returned to values close to baseline 5 days after eccentric contractions (Ochi et al. 2020; Ochi et al. 2021). In contrast, in animal studies, the reduced nerve function was present one week after eccentric contractions. Notably, in the animal studies the

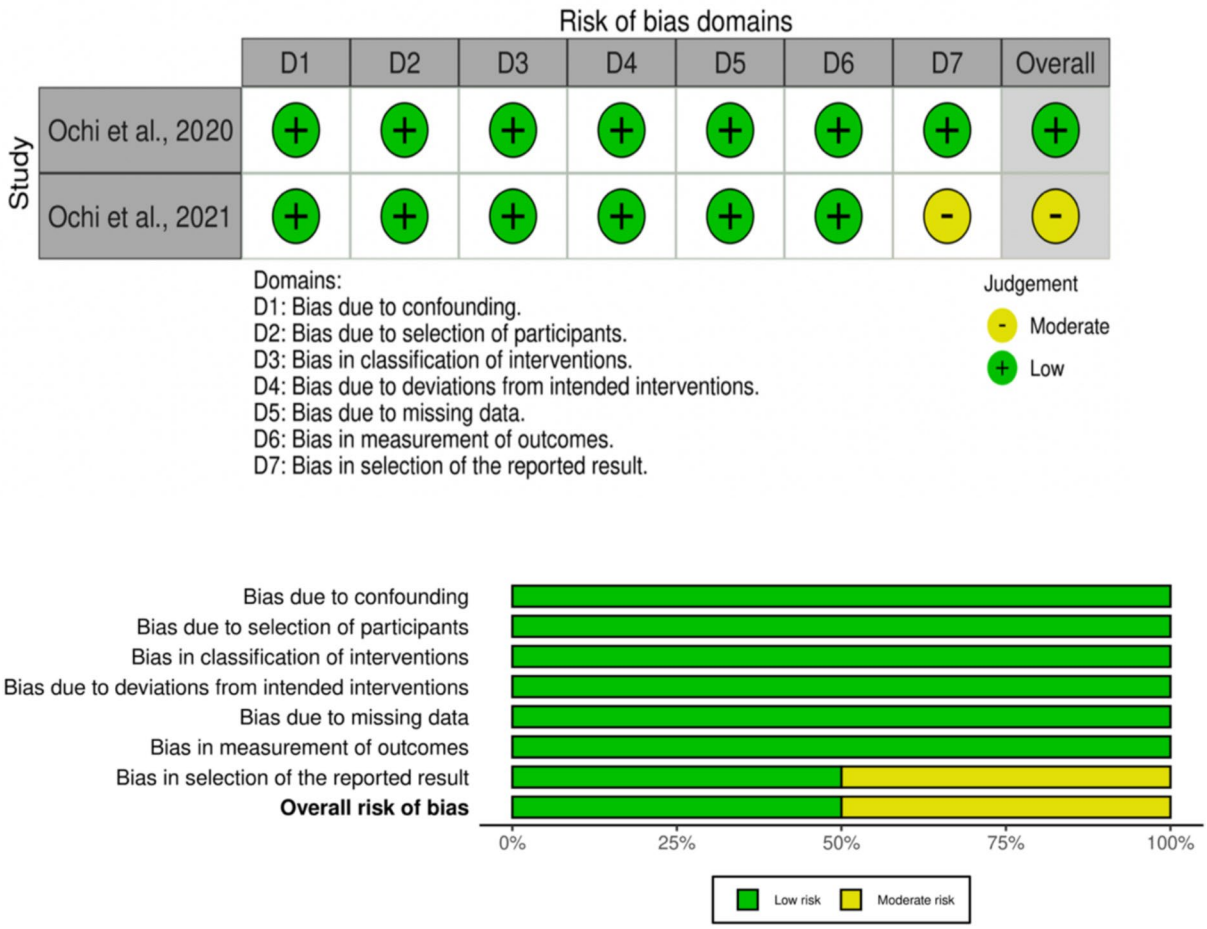

Fig. 3 Methodological quality of the human studies using the ROBINS-I tool

eccentric contractions were applied on the plantar flexors and the nerve assessed was the sciatic nerve. Possibly, the damage initially affected the tibial nerve, with subsequent extension to the sciatic nerve in the following days. Therefore, these temporal differences among animal and human studies could be related with the delay between muscle and nerve damage, the distinct methodologies of eccentric contractions, in addition to the variations in nerve characteristics that may influence the response to eccentric contractions (i.e., median and sciatic nerve vs animal and humans).

Animal studies revealed decreased nerve function just when eccentric contractions were performed at fast angular velocity (Lee et al. 2014; Kouzaki et al. 2016). Furthermore, it seems to be accentuated with accumulated bouts, as the decline in sciatic NCV increased from 21% (Lee et al. 2014) to 58% (Kouzaki et al. 2016), after one vs. four bouts, respectively. During high velocity eccentric contractions, several factors may affect the nerve's ability to maintain its function, since rapid stretch can drastically alter the behaviour of nerve tissue under load (Mahan et al. 2019) and increase the shear strain (Yoshii et al. 2011). At greater elongation rate, nerves exhibit increased stiffness and a decrease in their capacity to tolerate further elongation (Haftek 1970; Rydevik et al. 1990; Topp and Boyd 2006). The more severe the strain and strain rate to which the nerve is subjected, the greater the probability of injury due to reduced ability to return to its original length (Mahan et al. 2019; Singh et al. 2009; Wall et al. 1991). Findings from previous studies suggest that the degree of strain and strain rate play a role on the conduction of impulses by the nerve (Brown et al. 1993; Singh et al. 2009; Skoulis et al. 1998; Wall et al. 1992). As strain and strain rate increase, a decrease in NCV was observed (Skoulis et al. 1998). Thus, at slower stretch, NCV could be preserved for longer, explaining why such changes were not observed in the slow angular velocity eccentric contractions group. Furthermore, during high velocity eccentric contractions the muscle force increases, which can increase shear load on adjacent structures such as peripheral nerves. Notably, these changes on nerve function were accompanied by temporary strength loss, reaching greater magnitude after four

Table 2 Main characteristics of the included animal and human studies

Study	Sample characteristics	Groups and interventions		EC applied to	Outcomes	Nerve target	Immediate and short-term effects								
							Immediately after (i.e., <2 hours)	Short-term (i.e., <10 days)							
								1 Day	2 Days	3 Days	4 Days	5 Days	6 Days	7 Days	8 Days	10 Days
Lee et al., 2014	N=66, Male Wistar rats Age: 11 weeks Body mass: 285–358 g	20 EC (4 sets of 5 contractions)	at 30°/s	Gastrocnemius (by electrical stimulation) with forced dorsiflexion of the ankle joint (from 0° to 45°)	**Physiology:** p0 ED1 TrkC GAP-43 **Function:** Motor NCV	Sciatic				→ Motor NCV → p0, ED1, TrkC, GAP-43				→ Motor NCV → p0, ED1, TrkC, GAP-43		→ Motor NCV → p0, ED1, TrkC, GAP-43
			at 180°/s											↓ MNCV * ↓ p0 † • ↑ ED1** † ↑ TrkC # • ‡ → GAP-43		↑ MNCV ↑ p0 ↓ED1 ↓TrkC → GAP-43
Kouzaki et al., 2016	N=54, Male Wistar rats Age: 9 weeks old	1 bout of 20 EC (4 sets of 5 contractions) applied every 2 days (days 1, 3, 5, 7) - total of 4 bouts	at 30°/s		**Structure and morphology:** Myelin sheath thickness Fiber diameter **Function:** Motor NCV				→ NCV		→ Motor NCV		→ Motor NCV		→ Motor NCV → Myelin sheath thickness and Fiber diameter	
			at 180°/s								↓ Motor NCV *		↓ Motor NCV *		↓ Motor NCV * ↓ Myelin sheath thickness * and Fiber diameter *	
Ochi et al., 2020	N=12 young men; Age: 19.8 ± 1.7 years; Height: 172.4 ± 7.0cm; Body mass: 64.0 ± 8.6 kg	100 EC (10 sets x 10 contractions) at 60°/s		Flexor pollicis brevis muscle (by voluntary contraction). The metacarpophalangeal joint of thumb was extended from an ulnar adduction (0°) to a fully radial abduction position (90°)	**Function:** Motor NCV	Median	↓ Motor NCV *	↓ Motor NCV *	↓ Motor NCV *			↓ Motor NCV *				
Ochi et al., 2021	N=32 young men; Age: 19.6 ± 0.2 years; Height: 173.2 ± 1.2; Weight: 69.7 ± 1.9 kg; Body mass index: 22.0 ± 0.6				**Function:** Motor NCV Sensory NCV		↓ Motor NCV * ↓ Sensory NCV	↓ Motor NCV * ↓ Sensory NCV *	↓ Motor NCV * ↓ Sensory NCV *	↓ Motor NCV ↓ Sensory NCV *		↓ Motor NCV ↓ Sensory NCV *				

EC eccentric contractions; *ED1* macrophage-related protein; *GAP-43* growth-associated protein 43; *NCV* nerve conduction velocity; *p0* myelin sheath protein zero. Symbols: →: no change; ↓: decrease; ↑: increase

*denotes a significant (P<0.05) difference when compared to control group; **indicates a significant difference P<0.01, 180EC versus 30EC; # P < 0.05, 180EC group versus 30EC group; †P < 0.05, 180EC group on day7 versus 180EC group on day3;‡P < 0.01, 180EC group on day7 versus 180EC group on day3; •P < 0.01, 180EC group on day7 versus 180EC group on day10

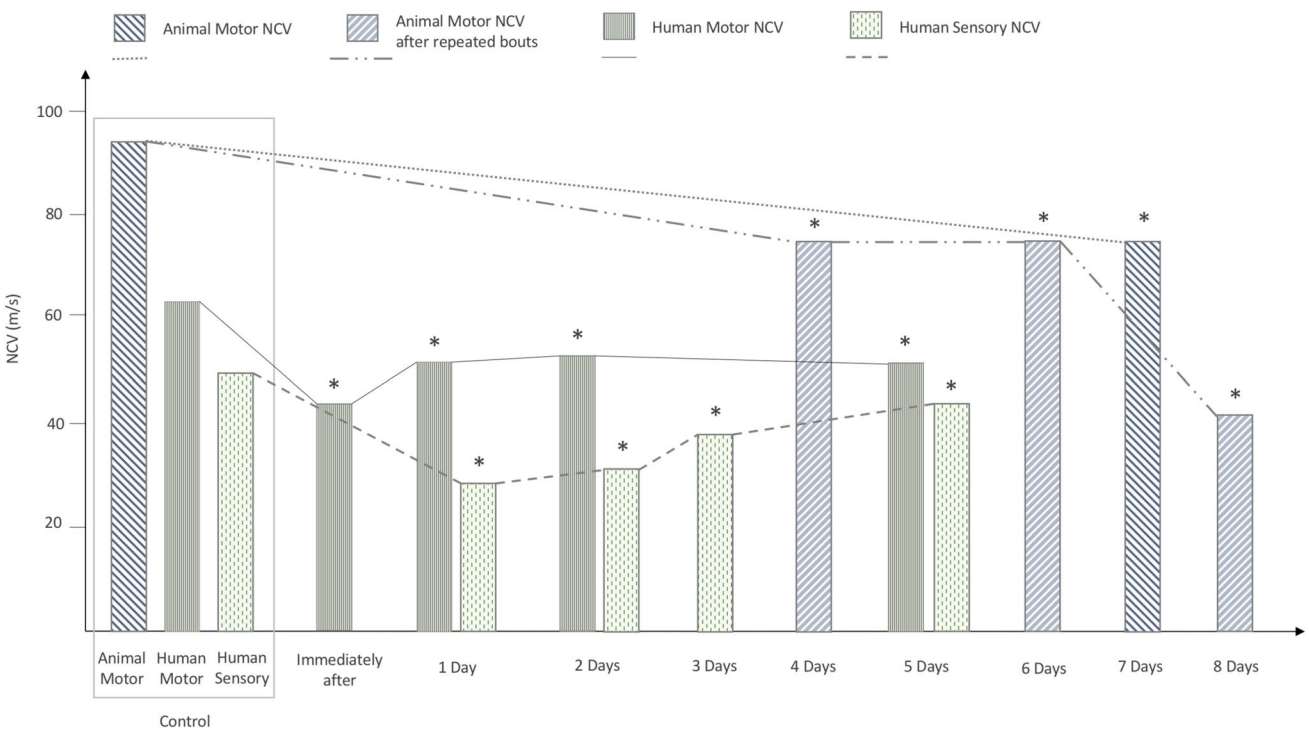

Fig. 4 Changes in nerve conduction velocity (NCV) across the included studies. * Denotes a significant ($p < 0.05$) difference at each time point between control group and eccentric contraction group

consecutive bouts at fast angular velocity (Kouzaki et al. 2016). This suggests that a potential association may exist between the effects on nerve function and strength loss, and should be explored in future investigations.

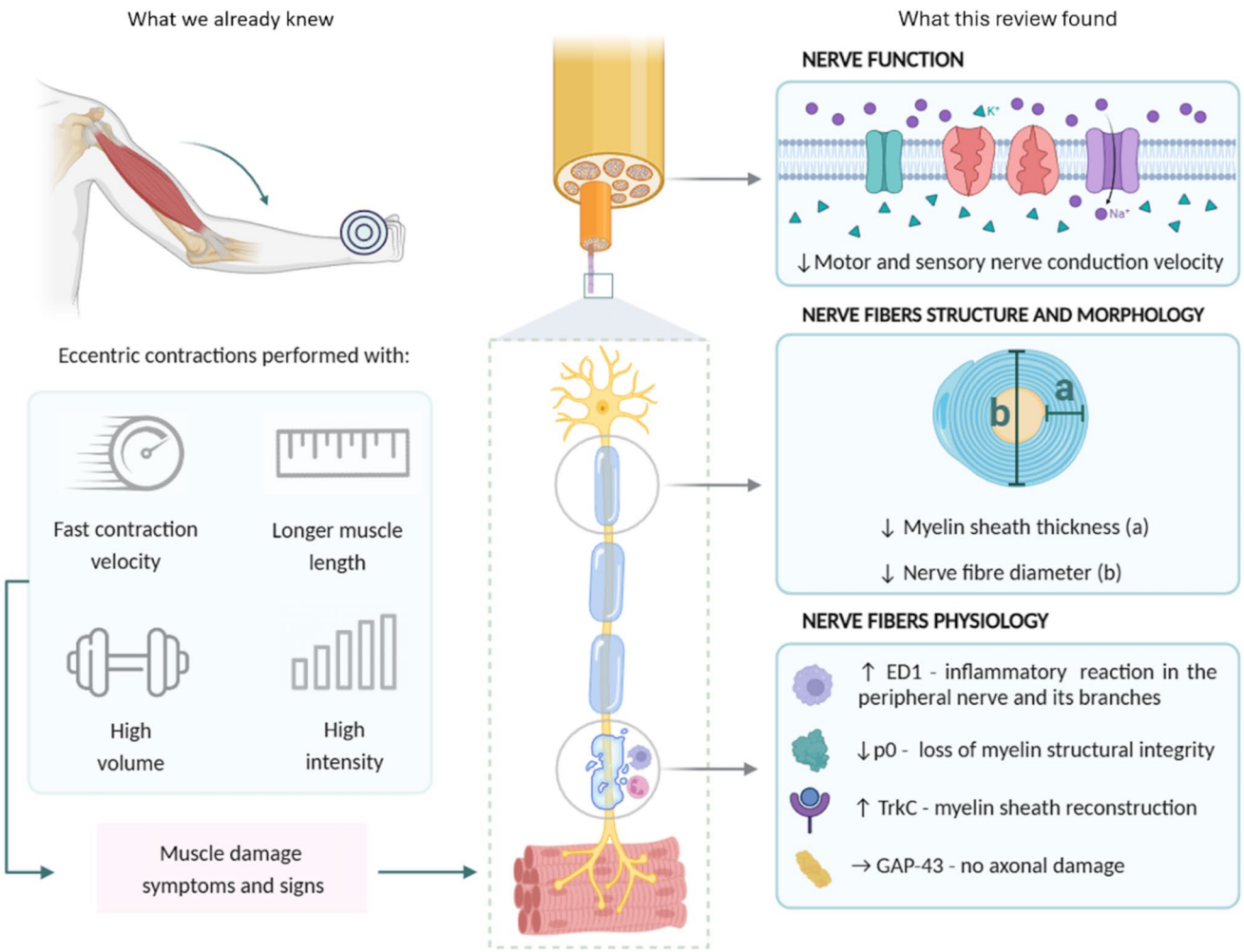

Fig. 5 The main findings regarding the effects of eccentric muscle contraction on peripheral nerve properties. Image created with BioRender (https://biorender.com)

Effects of eccentric contractions on nerve structure and morphology

Structural and morphological nerve alterations were observed at a microscopic level, such as decreased myelin sheath thickness and fibre diameter, after four repeated bouts of eccentric contractions at fast velocity (Kouzaki et al. 2016). These findings indicate potential neuronal tissue damage. The high angular velocity eccentric contractions possibly increase the strain rate at which the nerve is subjected compromising its physiological ability to accommodate, resulting in damage of structural components and consequent morphological alterations. Therefore, eccentric contractions inducing muscle strain might also damage nerve tissues. It is important to note that these structural and morphological changes may affect nerve function (Ikeda and Oka 2012), as the velocity of impulse transmission is influenced by the thickness of the myelin sheath, fibre diameter, and internode distance (Seidl 2014). Thus, the decreased myelin sheath thickness and nerve fibre diameter observed could explain the loss of nerve function due to reduced conductance of the action potential along the axonal length.

Effects of eccentric contractions on nerve physiology

The loss of myelin structural integrity can be manifested by physiological changes in the levels of protein concentration, besides the evidenced morphological and functional changes. Our results show variation in protein concentrations following eccentric contractions, especially p0, ED1, TrkC and GAP-43 (Lee et al. 2014).

Protein zero is considered the main myelin glycoprotein and the major protein component of peripheral nerve myelin (Eichberg 2002). Accentuate decline in p0 levels were detected on Day 7 after high velocity eccentric contractions,

being indicative of loss of myelin structural integrity and myelin sheath injury. Nevertheless, an increase was observed on Day 10, suggestive of myelin sheath restoration (Lee et al. 2014).

Our results have shown an increase in ED1 levels on Day 7, after fast velocity eccentric contractions. These findings are consistent with an inflammatory reaction in the peripheral nerve and its branches innervating the damaged muscle (Lee et al. 2014). Concomitant with inflammatory process, the increase in the neurotrophins synthesis and secretion of neurotrophic factors promotes the repair and regeneration of the myelin sheath (Yuan et al. 2021). Since higher levels of TrkC were detected in the myelin sheath on Day 7 than on Day 3, it suggests that TrkC were localised in Schwann cells around myelin and that the damaged myelin sheath is being repaired. The decrease observed in ED1 and TrkC concentration on Day 10 are indicative of resolution of the inflammation and complete myelin sheath reconstruction.

Depending on the severity of the injury, neurotrophic factors can activate also growth-associated proteins, such as GAP-43 (Chung et al. 2020). Considering that GAP-43 regulates the activities of regenerating axons, since no significant differences on GAP-43 levels were observed across the days, it is assumed that the damage induced by eccentric contractions did not extend to the axon (Lee et al. 2014).

Practical considerations

Although this topic is recent in the literature and requires further research, we speculate that it may have several implications in the fields of rehabilitation and sport. As immediate effects, the reduced nerve conduction velocity can impact neuromuscular function influencing the force production capacity and motor control. Understanding these effects is crucial for adjusting exercise intensity and activity levels, recovery programs, and injury prevention. However, the potential application of this topic is worthy of future investigation.

Limitations and recommendations for future research

This review is limited to the small number of animal and human studies for each outcome of interest. Due to the paucity and heterogeneity of the included studies, summarising the data quantitatively in a meta-analysis was not viable. Methodological weaknesses in the included animal studies were observed in some items due to the lack of adequate reporting of detailed information about the implemented methodology. The effects of eccentric contractions on nerve biomechanical properties and morphology at a macro scale level (measured by MRI and US) are still unexplored. Stronger evidence is needed to support our findings. Another aspect warranted to be examined is whether the exercise impacts myelinated and unmyelinated fibers equally, or even regions of the nerve that contain different proportions of connective tissue. Thus, further investigations examining the physiological mechanisms of peripheral nerve damage due to eccentric contractions are required. Importantly, studies should be from different laboratories to reduce potential bias factors.

Conclusions

This systematic review demonstrates that eccentric contractions induce immediate and short-term alterations to the peripheral nerve properties. High-velocity eccentric contractions led to a significant decrease in myelin sheath thickness and nerve fibre diameter. Concomitant physiological changes were found, such as a decrease of p0 and increase of ED1 and TrkC. Additionally, a decrease in motor and sensory NCV was consistently observed, with variations in the time course of these changes between animal and human studies. While this study provides valuable insights into transient peripheral nerve damage following eccentric contractions, it is important to acknowledge that definitive conclusions cannot be drawn at this stage due to the limited number of included manuscripts.

Appendix 1

See Table 3.

Table 3 Example of the search strategy

Search terms and their combination
Eccentric "nerve damage"
Eccentric "nerve injury"
Eccentric “nerve impairment”
Eccentric “nerve dysfunction”
Eccentric “nerve disorder”
Eccentric "nerve properties"
Eccentric exercise "neural adaptations"
Eccentric "nerve morphology"
Eccentric exercise "neural morphology"
Eccentric "nerve structure"
Eccentric exercise (epineurium or endoneurium)
Eccentric “myelin sheath thickness”
Eccentric “nerve sheath diameter”
Eccentric “nerve thickness”
Eccentric "nerve cross-sectional area"
Eccentric “nerve volume”
Eccentric “nerve mechanics”
Eccentric “neuromechanics"
Eccentric “nerve mechanical properties”
Eccentric "nerve strain"
Eccentric nerve (excursion or glide)
Eccentric "nerve stiffness"
Eccentric "nerve function"
Eccentric "nerve conduction"
Eccentric (nerve or neural) blood flow
Eccentric (nerve or neural) echogenicity
Eccentric “neuroinflammatory mediators”

Author contributions All authors developed the conception and study design. DL and TN conducted the literature search. DL and TN selected the articles for inclusion in the review. DL and TN independently rated the methodological quality of studies. All authors were involved in data interpretation, in revision and finalization for publication. All authors read and approved the final manuscript.

Funding No sources of funding were used to assist in the preparation of this systematic review.

Data availability The data supporting the findings of this study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest related to the content of this systematic review.

Ethical approval For this study, no ethical approval is required.

Consent to participate Not applicable.

Consent for publication Not applicable.

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