Abstracts and unpublished material were not included. Only manuscripts in English were reviewed. The PRISMA flow diagram (Fig. 1) illustrates the process by which the manuscripts were selected.

Inclusion Criteria

Studies examining the relation between stretching in humans and peripheral nerves or related aspects were included for review if they fulfilled the following selection criteria: 1) The studies were published up to December 2020; 2) the studies were published in peer review journals; 3) the studies examined the effects of stretching on nerves; 4) the studies had at least one measure regarding the nerve as outcome (Pre- or Post- intervention measures). Articles which have not evaluated stretching interventions, articles evaluating *in vitro* stretching of nerves, articles evaluating adaptations of the neural network and articles which considered surgical nerve elongation were not included in this study. The article screening was carried out by two independent investigators, who eventually resolved disagreements about article inclusion by negotiation. All duplicates were removed.

Data extraction

The selected manuscripts were included in the EndNote software (EndNote version X8; Thompson Reuters, New York, USA), to identify duplicates. These were manually checked in a second moment.

A Microsoft Excel (Microsoft Corp, Redmond, Washington) spreadsheet was compiled with the study's' relevant information: lead author, year of publication, sample size, stretch typology, location at which the stretching protocol was applied, the duration of the protocol (n° of stretching sessions), the analysed measures and the values of pre- and post- intervention. The data were extracted from any section of the manuscript. Figures were also used to extrapolate data through the WebPlotDigitizer (version 4.2) software, if relevant information for this review was not included in tables or the main text of the manuscripts.

Quality assessment

Quality of the studies was assessed by using the quality assessment tools from the National Heart, Lung, and Blood Institute (NHLBI) Available online at: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools (Accessed 30/12/2020); the choice for the applied tool was based on the study designs. Two independent investigators applied the NHLBI tools (APal and MB) and evaluated the items of the tools as "yes", "no", "not applicable", "cannot determine" or "not reported." This was used to guide the overall rating for the quality of each study as "good", "fair" or "poor." In case of disagreement, consensus was reached through discussion or by consulting a third author (AB). Supplementary Tables 1-3 have been provided with the results of the quality assessment.

Data analysis

The manuscripts included in the qualitative synthesis were classified for each nerve-stretch interaction retrieved. For each study, the primary and relevant information's were extracted. For each extracted variable, the mean difference between pre- and post- intervention was calculated. Percentage values and mean differences were used to describe relative changes between pre- and post- interventions.

Results

A total number of 8279 studies were identified through the preliminary search. Three additional records were also identified as relevant references. After title screening a total of 152 studies were deemed as potentially eligible. Sixty-six studies were removed as duplicates, leaving a total number of 86 manuscripts. These were screened and further application of inclusion and exclusion criteria lead to 22 pertinent manuscripts. The full text of these manuscripts was further analyzed and for the purpose of this review a total number of 10 articles were included (Figure. 1).

The 10 included manuscripts analysed the effects of stretching on peripheral nerve responses (Andrade et al., 2018; Andrade et al., 2020; Beltran-Alacreu et al., 2015; Coppieters et al., 2009; Echigo et al., 2008; Ellis et al., 2008; Gamelas et al., 2019; Jaberzadeh et al., 2005; Lee and Kim, 2017; Martinez-Paya et al., 2015) (Table 1).

The quality assessment revealed a "fair to good" overall methodological quality of the included records. One study was deemed as of "poor" methodological quality, four were deemed as "fair" methodological quality and three were deemed as "good" methodological quality. A breakdown for each study is provided in Supplementary Tables 1-3.

Our search strategy has identified only two studies which investigated direct anatomical modifications to peripheral nerves as a consequence of stretching (Andrade et al., 2018; Andrade et al., 2020). The remaining studies, however, evaluated other aspects closely related to the influence of stretching on the nervous structures. Therefore, the variables which were identified were: shear wave velocity (SWV), which is a measure of nerve stiffness; nerve displacement, which represents the movement of the anatomical structure of the nerve from resting position to the end point of a given movement; pain pressure thresholds (PPT) and visual analogue scale (VAS) both related to pain and resistive torque which was provided as a measure of pain onset. Since very few studies were retrieved no study subgrouping was performed.

Peripheral Nerve responses

The stretches targeted the median nerve (Coppieters et al., 2009; Echigo et al., 2008; Gamelas et al., 2019; Jaberzadeh et al., 2005; Martinez-Paya et al., 2015), the sciatic nerve (Andrade et al., 2018; Andrade et al., 2020; Ellis et al., 2008; Lee and Kim, 2017), the tibial nerve (Andrade et al., 2020) and posterior nerve cords (Beltran-Alacreu et al., 2015). High heterogeneity of stretching protocols was retrieved. Four studies performed neural gliding (Beltran-Alacreu et al., 2015; Coppieters et al., 2009; Echigo et al., 2008; Gamelas et al., 2019), two studies performed passive stretching modalities (Andrade et al., 2018; Lee and Kim, 2017), two studies performed neural mobilization (Ellis et

al., 2008; Lee and Kim, 2017), one study performed nerve tensioning (Gamelas et al., 2019), one study applied neurodynamic tests (Martinez-Paya et al., 2015), one study performed nerve directed stretching (Andrade et al., 2020) and one study a passive elbow extension (Jaberzadeh et al., 2005). The recruited participants were all healthy or asymptomatic except for the study of Lee and Kim (2017), who involved participants with radicular low back pain.

Nerve Stiffness

Two studies took into account SWV as a measure of nerve stiffness (Andrade et al., 2018; Andrade et al., 2020). In both studies SWV was assessed through ultrasound elastography. The first study (Andrade et al., 2018) had the aim of understanding if non-muscular structures, such as the sciatic nerve, could acutely influence ankle range of movement (ROM). As a result of the stretching intervention, stiffness of the sciatic nerve by decreased -13.3 ± 7.9% compared to baseline. The second study (Andrade et al., 2020) aimed to understand the chronic effect of nerve or muscle-directed stretching on tissue mechanics, resulting in a -19.7% decrease in the sciatic nerve stiffness and a –13.7% decrease in the tibial nerve stiffness, following the stretching intervention. In both studies the main findings result in decreased nerve stiffness following stretching (mean value across the studies, -15.6%). Table 2 summarizes the single study results.

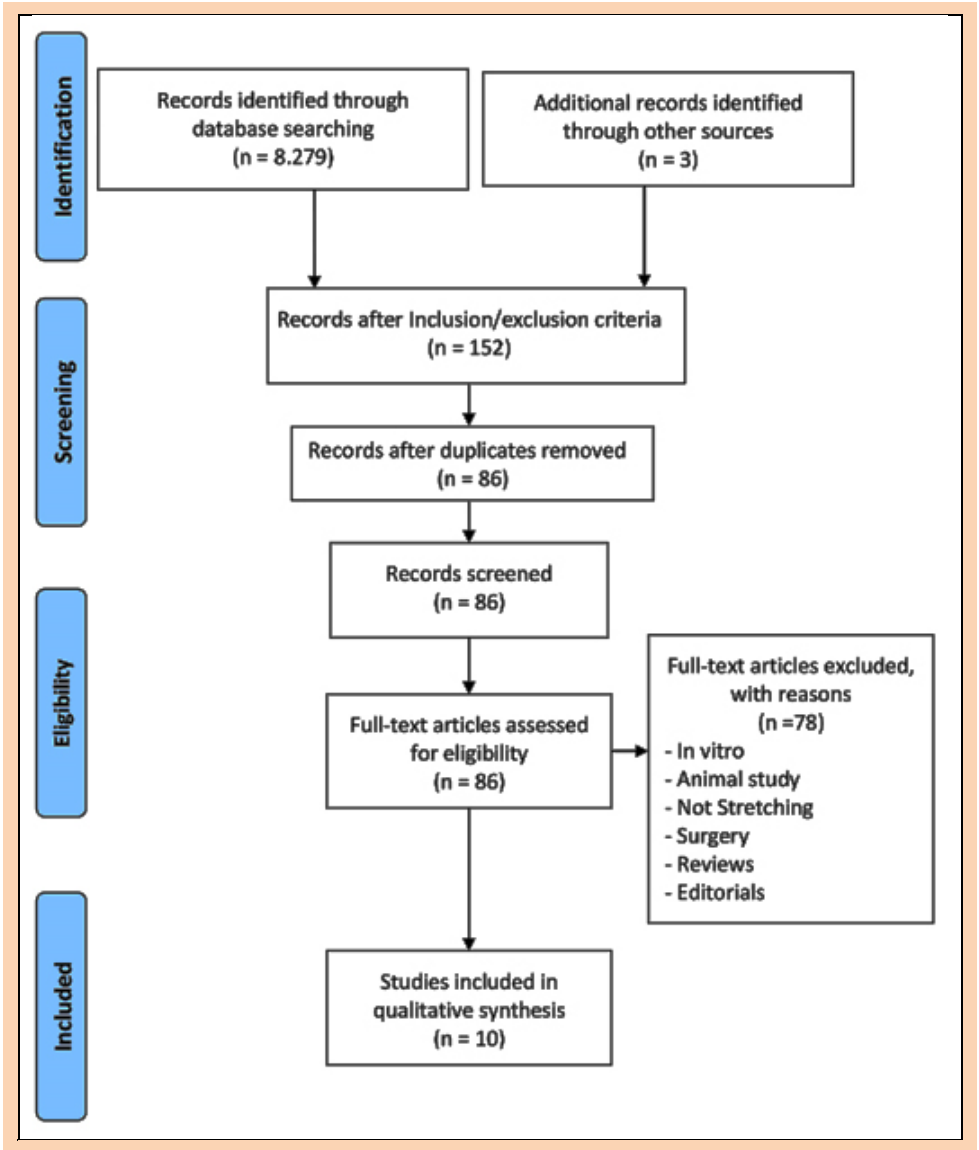

Figure 1. PRISMA flow diagram illustrating the process by which the manuscripts were selected.

Supplementary Table 1. Results of quality assessment of the NIH tool for observational cohort and cross-sectional studies

Author	Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Score
Andrade et al	2018	Y	Y	Y	Y	N	Y	Y	NA	Y	N	Y	Y	NR	Y	fair
Beltran-Alacreu et al	2015	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	NA	NA	Y	good
Coppieters et al	2009	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	NA	NR	Y	good
Echigo et al	2008	Y	Y	Y	CD	N	N	Y	N	Y	N	Y	NA	NR	Y	poor
Ellis et al	2008	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	NA	NA	Y	fair
Gamelas et al	2019	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	Y	good
Jaberzadeh et al	2005	Y	Y	Y	Y	N	N	Y	N	Y	N	Y	NA	NR	Y	poor
Martínez-Payá et al	2015	Y	Y	Y	Y	N	N	Y	Y	Y	N	Y	NA	Y	N	fair

Quality of included studies was assessed using the National Institutes of Health (NIH) Quality Assessment tool for Observational Cohort and Cross-Sectional Studies https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort). 1=Was the research question or objective in this paper clearly stated?; 2=Was the study population clearly specified and defined?; 3=Was the participation rate of eligible persons at least 50%?; 4=Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?; 5=Was a sample size justification, power description, or variance and effect estimates provided?; 6= For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?; 7=Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?; 8=For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?; 9=Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?; 10=Was the exposure(s) assessed more than once over time?; 11=Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?; 12=Were the outcome assessors blinded to the exposure status of participants?; 13=Was loss to follow-up after baseline 20% or less? 14=Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? CD=cannot be determined; NA=not applicable; NR=not reported; N=no; Y=yes.

Supplementary Table 2. Results of quality assessment of the NIH tool for case-control studies.

Author	Year	1	2	3	4	5	6	7	8	9	10	11	12	Score
Lee et al	2017	Y	Y	N	Y	Y	Y	Y	N	Y	Y	CD	N	fair

Quality of included studies was assessed using the National Institutes of Health (NIH) Quality Assessment tool for Case-Control Studies https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort). 1=Was the research question or objective in this paper clearly stated and appropriate?; 2=Was the study population clearly specified and defined?; 3=Did the authors include a sample size justification?; 4=Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?; 5=Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?; 6=Were the cases clearly defined and differentiated from controls?; 7=If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?; 8=Was there use of concurrent controls?; 9=Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?; 10=Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?; 11=Were the assessors of exposure/risk blinded to the case or control status of participants?; 12=Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis? CD=cannot be determined; NA=not applicable; NR=not reported; N=no; Y=yes.

Supplementary Table 3. Results of quality assessment of the NIH tool for controlled intervention studies.

Author	Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Score
Andrade et al	2020	Y	Y	Y	Y	Y	Y	Y	Y	CD	Y	Y	N	Y	Y	good

Quality of included studies was assessed using the National Institutes of Health (NIH) Quality Assessment tool for Controlled Intervention Studies https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort). 1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?; 2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?; 3. Was the treatment allocation concealed (so that assignments could not be predicted)?; 4. Were study participants and providers blinded to treatment group assignment?; 5. Were the people assessing the outcomes blinded to the participants' group assignments?; 6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?; 7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?; 8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?; 9. Was there high adherence to the intervention protocols for each treatment group?; 10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?; 11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?; 12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?; 13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?; 14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis? CD=cannot be determined; NA=not applicable; NR=not reported; N=no; Y=yes.

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Table 1. Synthesis of the studied pertinent to nerve responses to stretching.

Author	Year	Stretching	Protocol	N	Location	Duration	Measures	Assessment	Pre	Post
Andrade et al	2018	Passive	Ankle dorsiflexion	15	Sciatic Nerve	1 session	ROM, SWV	PS – 6 minutes	Resting conditions	ROM = 6.4 ± 2.6° SWV =-13.3±7.9%
Andrade et al	2020	Nerve directed stretching	Ankle dorsiflexion	21	Sciatic and Tibia Nerves	60 sessions	ROM, SWVs, SWSt	PS – 3 hours	ROM = 35.7 ± 6.6° SWVs = 6.1 ± 1.5 m/s SWVt = 7.3 ± 1.4 m/s	ROM =36.3 ± 6.1° SWVs = 4.9 ± 1.3 m/s SWVt = 6.3 ± 1.3 m/s
Beltran-Alacreu et al	2015	Neural gliding	Supine body flexion	45	Posterior Nerve Cords	1 session	PPT *(left side)*	PS – 5 minutes	M = 1.94 ± 0.14kg; T = 2.14 ± 0.54kg; SUB = 2.56 ± 0.88kg TRAP = 3.88 ± 0.88kg TIB = 5.18 ± 1.80kg	M = 2.52 ± 0.16kg; T = 2.31 ± 0.62kg; SUB = 3.01 ± 1.13kg TRAP = 4.17 ± 1.54kg TIB = 5.64 ± 1.89kg
Coppieters et al	2009	Neural gliding	Elbow extension + cervical ipsilateral flexion	15	Median Nerve	1 session	LNG	DS	Resting conditions	LNG = 10.2 ± 2.8 mm
Coppieters et al	2009	Neural tensioning	Elbow extension + cervical contralateral flexion	15	Median Nerve	1 session	LNG	DS	Resting conditions	LNG= 3.6 ± 2.3 mm
Echigo et al	2008	Neural gliding	Elbow extension with forearm supination	34	Median Nerve	1 session	LNG	DS	Resting conditions	LNG = 3.0 ± 1.81 mm
Echigo et al	2008	Neural gliding	Elbow flexion with forearm supination	34	Median Nerve	1 session	LNG	DS	Resting conditions	LNG = 3.0 ± 1.34 mm
Ellis et al	2008	Neural mobilization	Knee extension	27	Sciatic Nerve	1 session	LNM, PNM, LNG *Popliteal fossa*	DS	Resting conditions	LNM = 6.62mm PNM = 3.26mm LNG = 5.22mm
Gamelas et al	2019	Neural tensioning	4 sets - 10 reps with a 1 minute rest. Each repetition was performed at a rhythm of 6s.	15	Median Nerve	1 session	PPT, VAS *Th=Thenar Fr= Forearm*	PS – immediately	PPT Fr = 34.75 ± 14.41kg VAS Fr = 3.30 ± 1.76 PPT Th = 42.35 ± 15.8kg VAS Th = 3.83 ± 2.15	PPT Fr = 40.0 ± 13.77kg VAS Fr = 3.23 ± 2.01 PPT Th = 46.22 ± 15.72kg VAS Th = 3.27 ± 2.36
Gamelas et al	2019	Neural gliding	4 sets - 10 reps with a 1 minute rest. Each repetition was performed at a rhythm of 6s.	15	Median Nerve	1 session	PPT, VAS *Th=Thenar Fr= Forearm*	PS – immediately	PPT Fr = 39.11 ± 14.54kg VAS Fr = 3.60 ± 2.51 PPT Th = 46.38 ± 14.54 kg VAS Th = 3.67 ± 2.66	PPT Fr = 40.97 ± 14.25 kg VAS Fr = 3.43 ± 2.37 PPT Th = 47.89 ± 13.50 kg VAS Th = 3.57 ± 2.66
Jaberzadeh et al	2005	Elbow extension	Passive elbow extension	26	Median Nerve	1 session	RT	DS	RT =0.8 Nm Pain onset=3°	RT = 3.9 Nm Pain onset = 45°
Lee et al	2017	Passive stretching (s)	5 sets - 40 sec with a 20 second rest	22	Hamstrings	9 sessions	PPT, VAS, ROM, ODI	PS - 30 minutes	PPTs = 14.6 ± 2.9; VASs = 5.4 ± 0.8; ROMs = 46.3 ± 8.9 ODIs = 29.7 ± 8.9	PPTs = 17.3 ± 3.1; VASs = 2.1 ± 0.7 ROMs = 51.6 ± 9.7 ODIs = 17.8 ± 5.1
Lee et al	2017	Neural mobilization (nm)	5 sets 20 reps - 40 sec with a 20 second rest	22	Hamstrings	9 sessions	PPT, VAS, ROM, ODI	PS - 30 minutes	PPTnm = 14.5 ± 4.6; VASnm = 5.6 ± 1.0; ODInm =26.4 ± 4.9 ROMnm = 49.4 ± 10.7	PPTnm =18.4 ± 3.9; VASnm = 1.4 ± 0.8; ODInm =14.2 ± 3.8 ROMnm = 55.8 ± 10.2
Martínez-Payá et al	2015	Neurodynamic test	2 wrist flexions	22	Median Nerve	1 session	LNM, PNM, ND	DS	Resting conditions	LNM =32% (3.72mm) PNM =73% (1.58 mm); ND =14%

DS=During Stretching; LNG=Longitudinal nerve motion; LNM=Lateral nerve motion; M=Masseter; ND=Nerve deformation; N/A= Not Available; ODI= Oswestry Disability Index; PNM=Posterior nerve motion; PPT=Pressure pain thresholds; PS= Post Stretching; ROM=Range of movement; RT=Resistive torque; SUB=Suboccipitalis; SWVs= Sciatic nerve Shear wave velocity; SWVt= Tibial nerve Shear wave velocity T=Temporalis; TIB=Tibialis; TRAP=Trapezius; VAS=Visual analog scale.

Table 2. Results of the main parameters regarding nerve responses to stretching.

Author	Year	Location	N° of sessions	PPT (kg)	VAS	SWV (%)
Andrade et al	2018	Sciatic Nerve	1	/	/	-13.3
Andrade et al	2020	Sciatic Nerve	60	/	/	-19.7
Andrade et al	2020	Tibial Nerve	60	/	/	-13.7
Beltran-Alacreu et al ^{M}	2015	Posterior Nerve Cords	1	0.58	/	/
Beltran-Alacreu et al ^{T}	2015	Posterior Nerve Cords	1	0.17	/	/
Beltran-Alacreu et al ^{SUB}	2015	Posterior Nerve Cords	1	0.45	/	/
Beltran-Alacreu et al ^{TRAP}	2015	Posterior Nerve Cords	1	0.29	/	/
Beltran-Alacreu et al ^{TIB}	2015	Posterior Nerve Cords	1	0.46	/	/
Coppieters et al	2009	Median Nerve	1	/	/	/
Echigo et al	2008	Median Nerve	1	/	/	/
Ellis et al	2008	Sciatic Nerve	1	/	/	/
Gamales et al $^{Tensioning\ Th}$	2019	Median Nerve	1	5.25	-0.7	/
Gamales et al $^{Tensioning\ Fr}$	2019	Median Nerve	1	3.87	-0.6	/
Gamales et al $^{Gliding\ Th}$	2019	Median Nerve	1	1.51	-0.1	/
Gamales et al $^{Gliding\ Fr}$	2019	Median Nerve	1	1.86	-0.1	/
Jaberzadeh et al	2005	Median Nerve	1	/	/	/
Lee et al	2017	Sciatic Nerve	9	2.7	-3.3	/
Lee et al nm	2017	Sciatic Nerve	9	3.9	-4.2	/
Martínez-Payá et al	2015	Median Nerve	1	/	/	/
Mean			7.7	1.9	1.5	-15.6

Data are presented as the differences between pre and post intervention; PPT=Pressure pain thresholds; VAS=Visual analog scale; SWV= Shear Wave Velocity. SWV is presented as a % difference between pre and post intervention. ^{Fr}= Forearm region; ^{M} =Masseter; nm= Neural Mobilization; ^{SUB} =Suboccipitalis; ^{T} =Temporalis; Th = Thenar region; ^{TIB} =Tibialis; ^{TRAP} =Trapezius.

Nerve Displacement

Nerve displacement was measured for the sciatic and tibial nerves (Ellis et al., 2008) and for the median nerve (Coppieters et al., 2009; Echigo et al., 2008; Martinez-Paya et al., 2015) through ultrasound scannings.

In all studies the measures were collected before and at the end of each movement proposed by the authors. The results provide evidence of significant nerve displacement during movements, independently of their location. These movements occurred either transversally (6.62 mm for the sciatic nerve (Ellis et al., 2008) and 3.78 mm for the median nerve (Martinez-Paya et al., 2015) and longitudinally (5.22 mm for the sciatic nerve (Ellis et al., 2008) and 4.28 mm for the median nerve) and in some cases (in 14% of the population) a deformation of the nerve was observed. Table 2 summarizes the single study results.

Pain

Two standard measures of pain were provided by the authors, PPT (Beltran-Alacreu et al., 2015; Gamelas et al., 2019; Lee and Kim, 2017) and VAS (Gamelas et al., 2019; Lee and Kim, 2017). An additional measure was provided by Jaberzadeh et al. (2005), who calculated resistive torque together with joint angle as a measure of pain onset. The PPT measures were derived from two cross sectional studies (Beltran-Alacreu et al., 2015; Gamelas et al., 2019) and by a longitudinal study (Lee and Kim, 2017). The authors calculated PPT using an algometer at different anatomical locations (Two points in the masseter muscle, one in the temporalis muscle, one in the suboccipital area, one on the trapezius muscle and a distal point in the tibialis anterior muscle (Beltran-Alacreu et al., 2015), in the forearm, in an area innervated by the median nerve and in the thenar region (Gamelas et al., 2019) and finally in a pressure spot of the gluteus medius (Lee and Kim, 2017)).

All authors reported an increase in the PPT indicating increased pain tolerance after the stretching intervention (pre 18.9 ± 18.0 kg/cm^2 vs post 20.8 ± 19.2 kg/cm^2). Table 2 shows differences for each condition.

Measures of VAS were reported by two authors (Gamelas et al., 2019; Lee and Kim, 2017). In both studies a decrease in VAS measures was observed (mean pre- 4.2 ± 1.0 vs post- 2.8 ± 0.9).

The last study evaluating a measure of pain, determined the mechanosensitivity of the median nerve during a neurodynamic test (Jaberzadeh et al., 2005). The results of this study indicate that the median nerve was more sensitive to longitudinal stress and had an earlier pain onset during the neurodynamic test compared to a neutral position.

Discussion

The aim of the present study was to determine if stretching may elicit responses in peripheral nerves and our results suggest that these are present. In particular, nerve stiffness and pain sensitivity decrease and nerve displacement occurs in every movement plane, leading in some cases to nerve deformation.

Two studies by Andrade et al. (2018; 2020) were the only to have assessed anatomical adaptations to *in vivo*, acutely and chronically, measuring nerve stiffness through elastography. The studies report that stretching, decreased nerve stiffness (mean value across the two investigations, 15.6 ± 3.6%) without modifications of the stiffness of the surrounding muscles and this was significantly related to

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the increase in ROM of the stretched joint. Thus, underlining that peripheral nerves play a role in the ROM of a joint and that specific stretching modalities are also able to target peripheral nerves and not only muscles, which can acutely and chronically adapt to stretching.

It has to be noted that in the studies of Andrade et al. the measure of stiffness was assessed after the stretch intervention with the result of decreased stiffness, however if the measurement is performed during the stretching manoeuvre, the measures of nerve stiffness increase (Rugel et al., 2020; Zhu et al., 2018). In a study by Robinson and Probyn (2019) the authors have created a model describing the role of the sciatic nerve during hip flexion. The authors have calculated that in order to correctly accommodate hip flexion a minimum length of 64mm of sciatic nerve, between the center of the femoral head and the center of the sciatic nerve, is required in order for the nerve to turn around the femoral head. These findings confirm the biomechanical role of nerves during movement and stretching. However, nerve elasticity which mainly depends on the elastic and tensile properties of the perineurium, can accommodate tensile stress within certain ranges. Beyond such point the nerve will experience stress and will eventually arrive to mechanical failure (Sunderland, 1978). A direct nerve elongation without rupture can be performed within ranges of 6 to 20% of the original length of the nerve (Lundborg and Rydevik, 1973), while nerve vascularization can only be guaranteed until approximately 15.7% (Ogata and Naito, 1986). Excessive nerve elongation may result in a stretch lesion which can lead to neurological deficits, pain, neuroma formation and incomplete return to function in around 50% of cases (Yeoh et al., 2020). To this point a distinction between elastic and anelastic lesions must be underlined, with these latter resulting in more severe outcomes (Mahan et al., 2019; Mahan et al., 2020). Therefore, stretching modalities directed to peripheral nerves should consider these biomechanical aspects which also take into account nerve stiffness and compliance.

Evidence also exists relating increased stiffness of peripheral nerves to peripheral neuropathies as entrapment of the sciatic nerve, carpal tunnel syndrome or diabetic peripheral neuropathy (Stajic et al., 2018; Zakrzewski et al., 2019). Animal studies have also evaluated biomechanical responses of peripheral nerves to stretching, observing that 7 weeks were sufficient to increase nerve compliance if stretched within its physiological limits (Bora et al., 1980). Therefore, nerve stiffness modifications, are proportional to the viscoelastic properties of the nerve itself (Topp and Boyd, 2006).

Nerve displacement has been reported in both longitudinal and transversal directions. Neural mobilization (Martinez-Paya et al., 2015), neural gliding (Echigo et al., 2008) and neural tensioning (Coppieters et al., 2009) techniques were adopted within the included studies and in all cases displacements were observed. To be noted that in the study of Coppieters et al. (2009) a comparison between neural gliding and tensioning was performed, and greater nerve excursion was observed in the first of the two analysed conditions. The first segments of the nerve which experience movement are those close to the moved joint and if this latter continues its movement to greater ROMs, the nerve will start gliding more distantly from the point movement is applied (Topp and Boyd, 2006). However, peripheral nerves are usually lying in a slack position which allows the nerve to initially straighten and subsequently be exposed to tensile forces (Warner et al., 2020). This mechanism allows joint movements and ROM improvements beyond those (6 to 20%) above described (Behm, 2018). Another factors which influences nerve movement is the nerve bed length (Dilley et al., 2007). Shorter the bed length, less movement is observed and greater the tension the nerve will suffer during its lengthening. To be noted that nerves usually cross joints on the flexing side which preserves it from excessive lengthening. Two exceptions are the ulnar and sciatic nerve which cross their respective joints on the extensor side. As a result these are particularly susceptible to mechanical stress (Sunderland, 1978). A review analyzing nerve biomechanics (Topp and Boyd, 2006) describes the anatomical connections of peripheral nerves to outer connective tissues and how these interact to protect and fix the nerve to other anatomical surrounding tissues. Modifications of the connective tissue environment may cause nerve movement limitations, evoke pain or cause injury to the nerve (Stecco et al., 2019). Another recent systematic review has discussed the role of nerve excursion during limb movements, partially taking into account stretching studies. Within the study it is discussed that peripheral nerves have an enormous adaptability during movement, since the continuity of the nervous system through the body (Szikszay et al., 2017). However, the authors report that almost no investigation has examined specific adaptations of peripheral nerves after stretching interventions. Interestingly, when healthy populations are compared to pathological cohorts concerning nerve displacement, for example in entrapment pathologies as the carpal tunnel syndrome, these latter show reduced nerve excursion (Wang et al., 2014) often associated to pain. However, when interventions are carried to treat the pathology, nerve excursion increases and pain decreases (Schrier et al., 2019). Therefore, the adaptability of nerves to movement and stretching may have implications regarding the onset of pain (Schrier et al., 2019; Wang et al., 2014).

Our results have also shown that measures of pain decreased after the stretching maneuvers, for both PPT and VAS. The proposed interventions included passive stretching, neural mobilizations, neural gliding and nerve tensioning. It is important to highlight that one of the included studies evaluating measures of pain analyzed healthy and asymptomatic participants while the other study took into account a sample of people suffering from radicular low back pain. Greater reduction of the VAS score was seen in the radicular low back pain sample (Lee and Kim, 2017). It is unclear why pain sensitivity results decreased, however it is plausible that due to the mechanical action of stretching a post-synaptic inhibition, mediated by muscle spindles occurs (Lizis et al., 2020). Experimental studies have evaluated the effects of nerve stretches at different intensities indicating that increased internodal distance (~11%) is observed after a 10% nerve elongation. An increase in internodal distance is associated with increased conduction velocity along the nerve (Friede, 2017; Wu et

al., 2012) influencing its motor and sensory behaviours. However, when such stretch is applied to over relatively greater percentages, nerve conduction, first decreases and subsequently ceases (Wall et al., 1992). Findings which could provide explanation to the increased pain tolerance reported. Other possible theory regarding increased pain tolerance may be due to the presence along peripheral nerves, within their sheaths, of the *nervi nervorum*. These are smaller nerves innervating the nerve itself, very sensitive to stretches of their long axis (Bove and Light, 1997), which however become sensitive to pain following compression (Teixeira et al., 2016).

Despite the evidence this study reports, it is still premature to derive definitive conclusions, since it was possible to include only a confined number of manuscripts. In addition, all measures of pain were repeated at different anatomical locations, nevertheless on the same samples. It is however noteworthy, that the only study measuring pain outcomes by using a provocative pain test highlighted that perceived pain was greater during the provocative test than during a neutral stretch condition. The interpretation of this study may provide insight for future research in order to determine at which intensity a stretch can be provided without resulting in nerve injury in vivo.

Nerve responses to stretching seem to be related to modification in the viscoelastic properties of the nerve and its sheaths with the surrounding connective tissues.

Limitations of this review are the confined number of retrieved studies regarding peripheral nerve responses to stretching and the almost absence of longitudinal interventions. Future research needs to focus on these less considered aspects of stretching and provide anatomical and functional interpretation to adaptations of peripheral nerves to movement and in particular stretching.

Conclusion

The present review reports current evidence regarding responses of peripheral nerves to stretching, highlighting that nerve stiffness and pain pressure thresholds decrease. Therefore, both anatomical and functional aspects are involved as a consequence of stretching in peripheral nerves. Nerve displacement and nerve deformation were also frequently observed. Peripheral nerve responses need to be further verified.

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Key points

- Stretching decreases nerve stiffness.
- Peripheral nerves move and deform during stretching.
- Pain pressure thresholds increase following stretching.

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