



PENSAR EN MOVIMIENTO: Revista de Ciencias del
Ejercicio y la Salud

ISSN: 1409-0724

ISSN: 1659-4436

pensarenmovimiento.eefd@ucr.ac.cr

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Costa Rica

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CHRONIC EXERCISE ACROSS MUSCULOSKELETAL TISSUES: A SYSTEMATIC REVIEW [1]**

PENSAR EN MOVIMIENTO: Revista de Ciencias del
Ejercicio y la Salud, vol. 21, núm. 1, 2023, Enero-Junio
Universidad de Costa Rica
Montes de Oca, Costa Rica

DOI: <https://doi.org/10.15517/pensarmov.v21i1.55427>

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PENSAR EN MOVIMIENTO:

Revista de Ciencias del Ejercicio y la Salud

ISSN 1659-4436

Vol. 21, No.1, pp. 1 – 21

Abre 1° de enero, cierra 30 de junio, 2023

FULL STUDY OF CHARACTERISTICS OF MORPHOLOGICAL ADAPTATIONS IN RESPONSE TO CHRONIC EXERCISE ACROSS MUSCULOSKELETAL TISSUES: A SYSTEMATIC REVIEW

ESTUDIO COMPLETO DE ADAPTACIONES MORFOLÓGICAS EN RESPUESTA AL EJERCICIO CRÓNICO EN LOS TEJIDOS OSTEOMUSCULARES: UNA REVISIÓN SISTEMÁTICA

ESTUDO COMPLETO DE ADAPTAÇÕES MORFOLÓGICAS EM RESPOSTA AO EXERCÍCIO CRÔNICO NOS TECIDOS OSTEOMUSCULARES: UMA REVISÃO SISTEMÁTICA

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Envío original: 2022-06-18 Reenviado: 2023-01-06, 2023-04-21 Aceptado: 2023-04-26
Publicado: 2023-06-15

Doi: <https://doi.org/10.15517/pensarmov.v21i1.55427>

Editor asociado a cargo: PhD. Luis Fernando Aragón-Vargas

ABSTRACT

León, F., Mestre, A., Priego, L., & Vera, J.C. (2023). Full study of Morphological adaptations in response to chronic exercise across musculoskeletal tissues: a systematic review. **PENSAR EN MOVIMIENTO: Revista de Ciencias del Ejercicio y la Salud**, 21(1), 1-21. To date, there is no systematic review that summarizes the morphological adaptations of the musculoskeletal system in response to chronic exercise. This systematic review selected original articles

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published in English between 2000 and 2020, with a clear exercise intervention and presenting a morphological change in the tissue under study, and covering human participants irrespective of age, gender or health condition. In total, 2819 records were identified. After removal of duplicates, title and abstract screening and full-text review, 67 records were included in the final analysis (6 for inter-vertebral disc, 6 for cartilage, 36 for bone, 2 for ligament, 9 for tendon and 7 for muscle). The most used interventions were aerobic, resistance, and plyometric exercise. Population ranged from children and healthy active people to individuals with a health condition. In conclusion, as a response to chronic exercise there are morphological adaptations in the tissues of the musculoskeletal system which vary from increased stiffness to an increase in cross-sectional area. Although tissues can adapt, several questions still linger, such as optimal dose and type of exercise, whether adaptations can occur in an injured tissue, and functional implications of these adaptations. Future research should address these questions.

Keywords: Musculoskeletal system physiology, adaptation, morphology, lifestyle, physical activity

RESUMEN

León, F., Mestre, A., Priego, L. y Vera, J.C. (2023). Estudio completo de Adaptaciones morfológicas en respuesta al ejercicio crónico en los tejidos osteomusculares: una revisión sistemática. **PENSAR EN MOVIMIENTO: Revista de Ciencias del Ejercicio y la Salud**, 21(1), 1-21. Hasta la fecha, no existe una revisión sistemática que resuma las adaptaciones morfológicas del sistema osteomuscular en respuesta al ejercicio crónico. Esta revisión sistemática seleccionó artículos originales, con fecha de publicación de 2000 a 2020, idioma de publicación en inglés, con una clara intervención de ejercicio y que presentaron un cambio morfológico en el tejido estudiado. Participantes humanos independientemente de la edad, el género o condición de salud. Se identificaron 2819 registros. Después de eliminar los duplicados, la selección de títulos y resúmenes y la revisión de texto completo, se incluyeron 67 registros en el análisis final (6 para disco intervertebral, 6 para cartílago, 36 para hueso, 2 para ligamento, 9 para tendón y 7 para músculo). Los resultados destacan que las intervenciones más utilizadas fueron ejercicio aeróbico, contra resistencia y pliométrico. La población abarcó desde niños y personas sanas activas hasta personas con alguna condición de salud. Se concluye que como respuesta al ejercicio crónico existen adaptaciones morfológicas en los tejidos del sistema musculoesquelético, que pueden variar desde un aumento de rigidez hasta un aumento de área. Aunque los tejidos pueden adaptarse, aún quedan varias preguntas, como la dosis y tipo de ejercicio óptimo, si pueden ocurrir adaptaciones en un tejido lesionado y las implicaciones funcionales de estas adaptaciones. La investigación futura debe abordar estas preguntas.

Palabras clave: osteomuscular, adaptación, estilo de vida, actividad física.

RESUMO

León, F., Mestre, A., Priego, L. e Vera, J.C. (2023). Estudio completo de Adaptaciones morfológicas en respuesta al ejercicio crónico en los tejidos osteomusculares: una revisión sistemática. **PENSAR EN MOVIMIENTO: Revista de Ciencias del Ejercicio y la Salud**, 21(1), 1-21. Até o momento, não há uma revisão sistemática que resuma as adaptações morfológicas do sistema osteomuscular em resposta ao exercício crônico. Esta revisão sistemática selecionou artigos originais, com data de publicação de 2000 a 2020, idioma de publicação em inglês, com clara intervenção de exercícios e que apresentaram alteração morfológica no tecido estudado. Participantes humanos, independentemente da idade, sexo ou condição de saúde. Foram identificados 2.819 registros. Após eliminar os artigos duplicados, triagem de título e resumo e revisão do texto completo, 67 registros foram incluídos na análise final (6 para disco intervertebral, 6 para cartilagem, 36 para osso, 2 para ligamento, 9 para tendão e 7 para músculo). Os resultados destacam que as intervenções mais utilizadas foram exercícios aeróbicos, resistidos e pliométricos. A população variou de crianças e pessoas saudáveis ativas a pessoas com alguma condição de saúde. Conclui-se que, em resposta ao exercício crônico, ocorrem adaptações morfológicas nos tecidos do sistema musculoesquelético, que podem variar desde um aumento de rigidez até um aumento de área. Embora os tecidos possam se adaptar, várias questões permanecem, como a dose ideal e o tipo de exercício, se adaptações podem ocorrer no tecido lesado e as implicações funcionais dessas adaptações. Pesquisas futuras devem abordar essas questões.

Palavras-chave: osteomuscular, adaptação, estilo de vida, atividade física.

Appendix. Full study characteristics including authors, year of publication, study design, population, intervention, comparison and outcomes. Abbreviation list: IVD, intervertebral disc; RCT, randomized controlled trial; ADC, apparent diffusion coefficient; OA, osteo arthritis; BMD, bone mineral density; BMC, bone mineral content; FN femoral neck; CSA, cross sectional area; TSI, time since injury; ToA, total bone area; BSI, bone strength index; vBMD, volumetric bone mineral density; ACL, anterior cruciate ligament; PCL, posterior cruciate ligament; AT, Achilles tendon; PT, patellar tendon; AP, pennation angle; FL, fascicle length; VL, vastus lateralis.

Authors	Year	Study design	Population	Intervention	Comparison	Outcome
Intervertebral disc						
Belavy et al.	2019	Observational, cross-sectional	High volume road cyclist aged 25 to 35 (n= 36, 18 cyclist, 18 no sport)	No intervention	-No sport	-Higher IVD's in cyclist (0.75 mm, p=0.006) -Higher IVD T2 times in cyclist (10.5 ms, p=0.021)
Belavy et al.	2017	Observational, cross-sectional	Individuals aged 25 to 35 years of age (n= 79, 24 no sport, 30 joggers, 25 long distance runners)	No intervention	-No sport -Joggers (20-40 km) -Long distance runners (50+km)	-Higher IVD T2 times in joggers (+9.2%) and long distance runners (+11.4%) (p<0.01 compared to no sport) -Higher IVD's relative to vertebral body in joggers and long distance runners (p<0.05 compared to no sport)
Bowden et al.	2018	Observational, case control	Participants aged 35 to 55 (n=26, 15 daily vigorous activity, 16 high sedentarism, 14 more than 30 min of moderate to vigorous activity)	No intervention	-Daily vigorous activity -High sedentary -More than 30 minutes of moderate to vigorous activity	-Higher T2 values in T5/S1 (p=.004) in participants with any amount of daily vigorous activity
Khazadeh et al.	2020	Quasi experimental	Men with unilateral or bilateral lumbar and radicular leg pains due to lumbar disc herniation (n= 30, 15 suspension group, 15 conventional group)	Suspension exercise (8 weeks)	Conventional core stability exercise	No change in IVD height between groups

Owen et al.	2020	Single blinded RCT	Individuals with non specific chronic low back pain (n=40, 20 exercise, 20 control)	Resistance and aerobic exercise (6 months)	Control (manual therapy and motor control exercise)	No change in whole IVD T2 times, ADC and height between groups after controlling for false positives -Average lumbar IVD height relative to vertebral body height 7.6% greater than controls in basketball (p=.001) and swimming (p=.001) -Individual IVD height relative to vertebral body height greater than controls in basketball (6.3-14%, p≤.029) and swimming (7.6-15%, p≤010) -Individual IVD height relative to vertebral body height greater than controls at L2 to L3 in soccer (8.7%,p=0.36) and at L3 to L4 for baseball (7.6%, p=.011)
Owen et al.	2021	Observational, cross-sectional	Participants from a wide range of sports and non athletic controls (n=379,308 athletes, 71 control)	No intervention	-Sport (baseball, swimming, basketball, kendo, soccer, running) -No sport (control)	

Cartilage

Armagan et al.	2015	Prospective, randomized single blind	Ambulatory patients aged 45-70 years with idiopathic knee OA (n= 70, 30 home exercise, 40 glucosamine sulphate)	Home exercise program (6 months)	Glucosamine sulphate group	Improvement cartilage thickness (pretreatment 2.5 (0 min-4 max) post-treatment 2 (0 min -3 max), p<0.05) in medial femoral condyle in the home exercise group
Cotofana et al.	2010	RCT	Women aged 45-55 years of age (n=38, 18 endurance, 15 strength, 5 autogenic)	Exercise intervention (3 months)	-Strength training -Endurance training -Autogenic training (control)	No significant change in knee (patellar, medial tibia and medial femur) cartilage morphology

Hinterwimmer et al.	2014	Interventional, non randomized	Asymptomatic marathon beginners (n= 10, 5 males and 5 females)	Supervised running program and a marathon (6 month)	No comparison	- Lateral femur cartilage thickness decrease $1.7 \pm 1.6 \%$ (p = 0.010). - Lateral femur cartilage volume decrease $3.2 \pm 3.0 \%$ (p = 0.012)
Koli et al.	2015	RCT	Postmenopausal women with mild tibiofemoral OA (n=80, 40 exercise, 40 control)	Aerobic/step aerobic exercise (12 months)	No training (control)	Improvement in total patellar cartilage (baseline 47.9 (SD 7.9), post-treatment -3.8 (95% CI: -6.4 to -1.9), p=.018)
Küçük et al.	2018	Experimental, prospective comparative	Women with primary bilateral knee OA (n=45, 15 aerobic, 15 isokinetic, 15 isometric)	Exercise intervention (4 weeks)	-Isokinetic exercise -Aerobic exercise -Isometric exercise	Change in patellar cartilage volume (pre-treatment $2.24 \pm 0.29 \text{ mm}^3$ to $2.35 \pm 0.34 \text{ mm}^3$ post-treatment, p=0.036) in isometric group
Munukka et al.	2016	Two experimental arm RCT	Women aged 60-68 years with mild knee OA (n=87, 43 aquatic group, 44 control group)	Aquatic resistance training (4 months)	Usual care (control)	Decrease in T2 times (-1.2 ms, 95% CI:-2.2 to -0.2, p=0.021) in the aquatic group compared to controls in the medial femoral cartilage
Bone						
Alghadir et al.	2016	RCT	Healthy subjects aged 30-60 (n=100, 47 men 53 women)	Aerobic exercise (12 weeks)	No comparison	-Increase in BMD at the hip (normal 0.97 ± 0.18 , p<0.05, osteopenic 0.89 ± 0.1 , p<0.01, osteoporotic 0.98 ± 0.27 , p<0.01) -Increase in BMD at the spine (normal 0.96 ± 0.12 , p<0.05, osteopenic 1.6 ± 0.35 , p<0.01, osteoporotic 1.93 ± 0.45 , p<0.01)

Bailey & Brooke-Wavell	2010	RCT	Premenopausal woman (n= 85, 21 EX2, 22 EX4, 22 EX7, 20 CON)	Exercise intervention (6 months)	-Plyometric Exercise two days a week (EX2) -Plyometric exercise four days a week (EX4) -Plyometric exercise seven days a week (EX7) -Control (CON)	-Increase in femoral neck BMD group EX7(+1.7 (+0.7-2.7,) than in CON (-0.3 (-1.2-0.5), p= 0.003) and EX2(+0.2 (-0.8-1.2), p= 0.015)
		Cross sectional, descriptive	Healthy caucasian males (n=281)	No intervention	-Lifetime loading history (Low, mid, high tertile)	-Higher BMC at mid-femur in the mid (5.639± 0.590,p<0.05) and high (5.771± 0.658, p<0.01) tertile compared to low -Higher BMC at mid-tibia in the mid (4.266± 0.534, p<0.01) and high (p<0.001) tertile compared to low
Bailey et al.	2010	Single blind RCT	Post menopausal women with osteopenia (n=39, 19 EX, 20 CON)	Resistance, impact and balance, EX (52 weeks)	-Control (CON)	-Non-significant 0.5% increase in the EX group and a non-significant 0.9% loss in the CON group in total hip BMD -Mean difference in change between groups of -0.012 g/cm2 (95% CI -0.022 to -0.002 g/cm2, p= 0.02) at total hip BMD
Bolton et al.	2012	Prospective controlled study	Children aged 6-9 (n=2395, 808 INT, 1587 CON)	Standard physical activity classes (5 years)	-Daily physical education (INT,200 min/week) -Daily physical education (CON,60 min/week)	-Higher annual gain in spine BMD (0.045 (0.038, 0.050) p<0.001), FN BMC (0.36 (0.32, 0.40) p=0.02),and FN area(0.21 (0.18, 0.24) p=0.03) in INT girls compared to CON - Larger tibial cortical BMC (2.8 (2.7, 2.9) p=0.03), larger tibial cortical area (236 (225, 245) p=0.02), and larger radial CSA(130 (122, 139) p=0.04) in INT girls compared to CON -Higher annual gain in spine BMD (0.028 (0.025, 0.030)p=0.01) in INT boys compared to CON

Dowthwaite et al.	2007	Cross sectional, cohort	Premenarcheal gymnasts (n=56)	No intervention	-Gymnasts -Non-gymnasts	-Higher BMC at the ultradistal radius (0.90 (0.82–0.98), $p \leq 0.001$), areal BMD (0.365 (0.343–0.386), $p \leq 0.001$), mean periosteal width 16.20 (15.43–16.96), $p < 0.05$ at the ultradistal radius in the gymnast group -Higher BMC (1.09 (1.03–1.16), $p \leq 0.001$), areal BMD (0.511 (0.487–0.535), $p < 0.05$), mean periosteal width (10.62 (10.23–11.01), $p \leq 0.001$), and cortical cross sectional area (53.76 (50.66–56.86), $p \leq 0.001$) at 1/3 distal radius in the gymnast group
Draghici et al.	2019	Cross sectional, cohort	Men with SCI (n=13)	FES rowing	No comparison	-Interaction between total distance rowed, TSI and peak foot force in trabecular thickness ($R^2=0.72, p < 0.01$)
Du et al.	2021	RCT	Post-menopausal women (n=10)	High impact unilateral exercise (6 months)	No comparison	-Increase in trabecular number (baseline 1.70 ± 0.13 , post intervention 1.78 ± 0.20 ; time $\times$ leg interaction $p = 0.043$)
Ducher et al.	2004	Cross sectional	Regional level tennis players (n=57, 33 men, 24 women)	No intervention	-Distal ulna and radius from playing arm -Distal ulna and radius from non playing arm	-Higher BMC total in radius ($14.98 \pm 7.03, p < 0.0001$) and in ulna ($13.44 \pm 7.36, p < 0.0001$) in the playing arm
Ducher et al.	2011	Cohort, prospective	Competitive female tennis players aged 10 to 17 (n=45, 13 premenarcheal (pre/peri), 32 postmenarcheal (post))	Tennis playing (12 months)	-Distal ulna and radius from playing arm -Distal ulna and radius from non playing arm	-Increase in the pre/peri group in BMC ($20.6 \pm 10.0, p < .001$), ToA ($11.7 \pm 6.6, p < .001$) and CoA ($19.9 \pm 11.7, p < .001$) in the playing arm compared to the non playing arm -Increase in the post group in BMC ($19.2 \pm 10.2, p < .001$) and ToA ($10.1 \pm 5.0, p < .001$) in the playing arm compared to the non playing arm

Ducher et al.	2009	Cross sectional, descriptive	Pre, peri and postpubertal competitive male tennis players (n=43)	No intervention	-Tennis(sport)	-Higher cortical area ($35.6 \pm 10.3, p < 0.01$) in prepubescent vs peripubescent boys -Higher cortical area ($66.1 \pm 18.6, p < 0.01$) in postpubescent vs peripubescent boys
Greene et al.	2009	RCT	Prepubertal girls aged 6-10 (n=42, 13 CON, 13 LD, 13 HD)	Single leg drop landing exercise (8 months)	-Low drop 14 cm (LD) -High drop 23 cm (DP) -Control (CON)	- No change in osteogenic adaptations in bone geometry, biomechanical properties or bone strength index -Increase in HiRIT in FN medial cortical thickness compared with CON ($5.6 \pm 1.7\%$ versus $-0.1 \pm 1.9\%$, $p = 0.028$) and IAC ($5.6 \pm 1.7\%$ versus $0.7 \pm 1.7\%$, $p = 0.044$) -Improvement in FN cortical volume ($0.09 \pm 0.05 \text{ cm}^3$, $p = 0.041$) in HiRIT -improvement in HiRIT compared to CON for distal tibia total BMC ($0.1 \pm 0.3\%$ versus $-3.0 \pm 0.4\%$, $p < 0.001$), total vBMD ($0.0 \pm 0.3\%$ versus $-0.8 \pm 0.3\%$, $p = 0.050$), total area ($0.0 \pm 0.4\%$ versus $-2.1 \pm 0.5\%$, $p = 0.001$), total BSI ($0.1 \pm 0.4\%$ versus $-3.9 \pm 0.5\%$, $p < 0.001$), trabecular BMC ($0.4 \pm 0.4\%$ versus $-1.8 \pm 0.5\%$, $p = 0.001$), trabecular area ($0.2 \pm 0.5\%$ versus $-1.6 \pm 0.5\%$, $p = 0.013$), and trabecular BSI ($0.7 \pm 0.5\%$ versus $-1.9 \pm 0.6\%$, $p = 0.001$)
Harding et al.	2020	Semi-randomized RCT	Middle-aged and older men ≥ 45 years of age with osteopenia or osteoporosis (n=93, 34 HiRIT, 33 IAC, 26 CON)	High intensity progressive resistance and impact training, HiRIT (8 months)	-Isometric axial compression (IAC) -Control (CON)	-Increase in distal forearm BMC ($2.14 \pm 0.34, p = 0.04$) in INT girls compared to CON girls
Hasselstrøm et al.	2008	Non-randomized RCT	Pre-school children (n=379, 135 boys and 108 girls INT, 62 boys and 76 girls CON)	Standard physical activity classes (3 years)	-Standard physical activity classes with higher volume (180min/week, INT) -Standard physical activity classes with	-Increase in distal forearm scanned area (7.42 ± 0.82 , $p = 0.005$) in the INT girls compared to CON girls

					normal volume (90 min/week, CON)	
Heinonen et al.	2002	Observational, cross sectional	Female national and international level weightlifters and powerlifters (n=14, 14 CON)	No intervention	-National and international level weightlifters and powerlifters - Aged matched, relatively active (CON)	-Difference in distal femur total density (301.2 (30.0), p=0.040) in favour of the weightlifting group -Difference in cross sectional area at the distal radius (101.9(28.0),p= 0.029) and in the radial shaft (88.8 (16.5), p=0.001) in favour of the weightlifting group -Difference in cortical wall shaft in the radial shaft (3.6 (0.46), p=0.037) in favour of the weightlifting group -Difference in cortical area at the tibial midshaft (305.7(35.0), p=0.034) in favour of the weightlifting group
Hughes et al.	2018	Observational, longitudinal	U.S. army female recruits (n=91)	Basic combat training (8 weeks)	No comparison	-Increase in mean trabecular thickness [1.13% (0.76, 1.50); p < 0.001], trabecular number [1.21% (0.48, 1.94); p < 0.05], trabecular bone volume/total volume [1.87% (1.31, 2.43); p < 0.001], trabecular BMD [2.01% (1.44, 2.58); p < 0.001], and cortical thickness [0.98% (0.38, 1.58); p < 0.001] at the tibia
Karinkanta et al.	2007	RCT	Women aged 70-79 (n= 149, 37 RES, 37 BAL, 39 COMB, 37 CON)	Exercise intervention (12 months)	-Resistance training group (RES) -Balance-jumping training group (BAL) -Resistance training and balance-jumping training (COMB)	-No effect in BMD at femoral neck or tibial shaft

				-Non-training control group (CON)	
Kukuljan et al.	2011	RCT	Healthy males aged 50-79 (n= 180,45 EX+FM, 46 EX, 45 FM, 44 CON)	Exercise intervention and supplementatio n (18 months)	-Exercise plus fortified milk (EX+FM) -Exercise (EX) -Fortified milk (FM) -Control (CON)
			-Increase in femoral neck BMD [1.9% (95% CI, 1.2, 2.5)], CSA [1.8% (95% CI, 0.8, 2.7)] in the exercise group -Increase in lumbar spine trabecular BMD [2.2% (95% CI, 0.2, 4.1)] in the exercise group -Improvement in BMD in the dominant radius for both IT (0.033±0.015 g/cm2, p= 0.046) and RT (0.037±0.014 g/cm2, p= 0.015) -Improvement in trabecular (1.86 ± 0.90 % versus -1.30 ± 0.81%, p= 0.029), distal radius (8.55 ± 2.26% versus 1.50 ± 2.04%, p= 0.040) and total BSI bone strenght index (15.35 ± 2.83% versus 2.67 ± 2.55%, p = 0.005) density in the non dominant limb in the IT group compared to RT -Improvmnt in cortical content (2.63 ± 1.08 mg, p= 0.025), density (29.53 ± 7.70 mg/cm3, p= 0.001) and cortical thickness (0.06 ± 0.02 mm, p= 0.019) in the non dominant limb in the RT group compared to IT		
Lambert et al.	2020	Single blind RCT	Inactive healthy young adult women aged 18-30 (n=22, 10 impact training, 12 resistance training)	Two exercises regimes (10 months)	-High intensity progressive impact training (IT) -High intensity progressive resistance training (RT)
		-Improvement for dominant FN trabecular BMC (9.64 ± 5.29% versus -10.74 ± 5.86%, p= 0.024), total BMC (8.06 ± 5.22% versus -11.15 ± 5.77%, p = 0.030),and cortical BMD (3.68 ± 1.99% versus -4.14 ± 2.20%, p = 0.021) in the RT group compared to the IT			

						-Improvement in dominant tibial shaft cortical area ($3.41 \pm 1.31 \text{ mm}^2$, $p = 0.017$), periosteal circumference ($0.38 \pm 0.15 \text{ mm}$, $p = 0.018$) in the RT group -Improvement in cortical thickness for both RT ($0.05 \pm 0.02 \text{ mm}$, $p = 0.021$) and IT ($0.05 \pm 0.02 \text{ mm}$, $p = 0.047$)
Lang et al.	2014	Prospective, non randomized	Healthy men and women (n=22, 8 ABBAD, 7 SQDL, 7 COMBO)	Exercise intervention (16 weeks)	-Standing hip abduction/adduction (ABADD) -Squat/deadlift (SQDL) -Combination (COMBO)	-Increase in the volume of the trochanteric cortical region (4.1%, $p < 0.01$) in the ABADD group -Increase in integral vBMD, cortical vBMD, and cortical volume (1.6% to 3.4%, $p < 0.05$) in the SQDL group in the femoral neck -Increase in vertebral integral BMD (3.1%, $p < 0.05$) and spinal trabecular BMD (7.0%, $p < 0.05$) in the SQDL group
Marques et al.	2013	Prospective, non randomized	Caucasian older adults (n=40, women 20, 20 men)	Exercise intervention (resistance and odd impact, 32 weeks)	No comparison	-Increase trochanteric (0.648 ± 0.080 women, 0.774 ± 0.114 men, $p < 0.001$) intertrochanteric (1.041 ± 0.139 women, 1.172 ± 0.163 men, $p = 0.005$) total hip (0.872 ± 0.111 women, 1.006 ± 0.138, $p = 0.001$) lumbar spine (0.896 ± 0.129 women, 1.065 ± 0.172 men, $p =$

						<0.001) and FN (0.705±0.104 women, 0.821±0.115 men, p=0.002) BMD
Marques et al.	2011	RCT	Caucasian older women (n=60, 30 ET, 30 CON)	Multicomponent exercise training (8 months)	-Exercise training (ET) -Control (CON) -Exercise (EX) -No exercise, no HRT (NO)	-Increase in BMD FN (0.717±0.085, p=0.008) in the ET group
Milliken et al.	2003	Prospective, comparative	Postmenopausal women with and without HRT (n=94, 26 EX, 30 NO, 17 EX+HRT, 21 HRT)	Exercise intervention and hormone therapy (12 months)	-Exercise+ HRT (EX+HRT) -No exercise, HRT (HRT)	-Increase in BMD at the greater trochanter (3.0 ± 7.7, p= 0.03) in the EX+HRT at 12 months -Increase in BMD at Ward's triangle (1.0 ± 8.7, p= 0.04) in EX at 12 months
Morse et al.	2019	Comparative RCT	Non ambulatory men and women with SCI (n=69, 35 EX, 34 EX+ZA)	Exercise intervention and supplementation (12 months)	-Functional electrical stimulation rowing exercise (EX) -Functiona electrical stimulation rowing exercise + Zoledronic acid (EX+ZA)	-Greater CBV in proximal tibia metaphysis (345±109 mm ³ , p=0.006) and in distal femoral metaphysis (471±225 mm ³ , p=0.05) in EX+ZA compared to EX
Nilsson et al.	2013	Observational, cross sectional	Active men (n= 361, 106 RE, 78 SC, 177 CON)	No intervention	-Resistance exercise (RE) -Soccer (SC) -Non exercise (CON)	-Higher BMD at FN (1.26±0.17p<0.001) lumbar spine (1.36±0.15, p<0.001) larger cross sectional cortical size at the tibia (310±34, p<0.001) trabecular number (2.25±0.27, p<0.001) trabecular thickness (90.8±11.0p<0.001) in SC group

O'Leary et al.	2019	Observational, longitudinal	British male infantry recruits (n=42)	British Army's infantry basic military training course (13 weeks)	No comparison	-Increase in areal BMD for total body (P = 0.031, dz= 0.36) and arms (P = 0.001, dz= 0.57) -Increase in total BMD(dominant leg 351± 41, p< 0.05, non-dominant leg 233± 25, p< 0.05) trabecular BMD(dominant leg 232± 25, p< 0.05, non-dominant leg 233± 25, p< 0.05) and cortical BMD(dominant leg 888± 26, p< 0.05, non-dominant leg 896± 26,p< 0.05)
Pang et al.	2006	RCT	Community dwelling individuals with stroke (n=63, 32 INT, 31 CON)	Intensive exercise program (19 weeks)	-Aerobic, balance and resistance exercise (INT) -Upper extremity exercise(CON)	-Increase in trabecular BMC (231.9±56.,p=0.048) in the INT group compared to the CON -No significant region-by-exercise group interactions (F= 1.587, P= 0.140) in the mean radial cortical BMD -OI groups had 1.5 to 2.6% (p<0.05) lower cortical BMD than referents at all four sectors (posterior, lateral, anterior and media) at the tibial shaft -RLI group had 1.0% lower BMD at the anterior sector (p<0.05) than referents at all four sectors (posterior, lateral, anterior and media) at the tibial shaft -HM group had 1.2% lower BMD at the lateral sector (p<0.05) than referents at all four sectors (posterior, lateral, anterior and media) at the tibial shaft
Rantalainen et al.	2011	Observational, cross sectional	Premenopausal women athletes (n=180, 60 HI, 47 OI, 15 HM, 16 RLI, 42 RNI) and 41 non athletic referent	No intervention	-High impact sport (HM) -Odd impact sport (OI) -High magnitude sport (HM) -Repetitive, low impact sport (RLI) -Repetitive, non impact (RNI) -Non athletic	

Specker & Binckley	2003	Randomized, placebo controlled, partially blinded	Children aged 3-5 (n=239, 57 FMC, 57 FMP, 62 GMC, 62 GMP)	Exercise plus supplementation or placebo (1 year)	-Fine Motor+ Calcium (FMC) -Fine Motor+Placebo (FMP) -Gross Motor+Calcium (GMC) -Gross Motor+Placebo (GMP)	-Increase in leg BMC in GMC (40.9±1.3, p=0.05) group compared to other groups -Increase in periosteal (49.5±0.7 GMC, 49.9±0.7 GMP, p= 0.03) and endosteal (40.7±0.9 GMC, 41.7±0.9 GMP, p=0.05) circumference in both GMC and GMP compared to other groups -Increase in midfemur bone circumference 0.2% (95% CI: 0.01% to 0.35%; p= 0.033) in the EX group compared to CON -Subjects in the highest quartile (> 66 exercise sessions during the 12 months) showed a 1.2% (95% CI: 0.2 to 2.2; p= 0.03) gain in bone circumference and a 0.5% (95% CI: 0.0 to 0.9; p= 0.04) gain in cortical CSA compared to the subjects in the lowest quartile (< 19 sessions) at proximal tibia
Vainionpää et al.	2007	RCT	Women aged 35 to 40 (n= 5161, 60 EX, 60 CON)	Impact and plyometric exercises EX (12 months)	-Control (CON) -Physical activity in the Swedish school curriculum with higher volume (40min/day, INT)	-Higher BMC in lumbar spine (2.4 ± 1.1, p=0.01) and L3 (.94 ± 0.63, p<0.001) in the INT group compared to the CON group -Higher BMD in the lumbar spine (0.044 ± 0.0, p<0.001) and L3 (0.047 ± 0.0, p<0.001) in the INT group compared to the CON group
Valdimarsson et al.	2006	Prospective non randomized	School aged girls (n=103, 53 INT, 50 CON)	Ordinary physical activity in the Swedish school curriculum (1 year)	-Physical activity in the Swedish school curriculum with higher volume (60min/week, CON)	-Higher bone width in L3 (0.17 ± 0.12, p<0.001) in the INT group compared to the CON group
Watson et al.	2015	Single blind RCT	Postmenopausal women aged 60+ with	High-intensity progressive resistance	-Control (CON)	-Improvement FN BMD (0.3±0.5 % vs -2.5±0.8 %, p=0.016) and LS BMD (1.6±0.9 % vs -1.7±0.6 %, p=0.005) in the HiPRT group

			low bone mass (n=28, 12 HiPRT, 16 CON)	training HiPRT (8 months)		
Winters-Stone et al.	2014	Single blind RCT	Men with prostate cancer (n= 51, 29 POWIR, 22 FLEX)	Progressive, moderate-intensity resistance + impact training, POWIR (12 months)	-Flexibility training (FLEX, used as control)	- Preservation of L4 BMD in the POWIR group (-0.4%, p=0.03) compared to loss (-3.1%) in controls (FLEX)
Winters-Stone et al.	2013	RCT	Women breast cancer survivors with treatment related menopause (n=71, 35 POWIR, 35 FLEX)	Progressive, moderate-intensity resistance + impact training POWIR (12 months)	-Flexibility training (FLEX, used as control)	-Change in both spine (ITT results—coefficient on slope of time 0.009, SE 0.004, t(48) 02.21, p=0.032) and femoral neck BMD (ITT results—coefficient on slope of time 0.011, SE 0.004, t(48) 03.19, p=0.004) among women with 1+ years past onset of menopause in the POWIR group
Winters-Stone, Snow	2006	Prospective, non randomized	Premenopausal woman (n= 35, 19 LOWER, 16 UPPER+LOWER, 24 CON)	Exercise intervention (12 months)	-Lower body resistance plus jumping exercise (LOWER) -Upper and lower body resistance plus jumping exercise (UPPER+LOWER) -Control (CON)	-Increase in greater trochanter in UPPER+LOWER (2.2± 2.8, p< 0.05) and LOWER (2.6± 2.5, p< 0.05) compared to CON -Increase in spine BMD in UPPER+LOWER (1.3± 3.7, p< 0.05.) compared to CON and LOWER
Wochna et al.	2019	Non-randomized RCT	Post-menopausal women aged 54-65 (n=18, 9 T, 9 CON)	Aqua fitness training (6 months)	-Aqua fitness training (T) -No physical activity (CON)	-No effect in in BMD at left hip, lumbar spine or whole body

Ligament



Grzelak et al.	2012	Observational, descriptive	Male weightlifters and age matched controls (n=28, 9 W, 19 CON)	No intervention	-Weightlifting (W) -Age matched control (CON)	-Higher mean cross sections in W (71.7, 52.9–111.2) than CON (40.56, 23.83–59.1) for ACL -Higher mean cross sections in W (64.48, 52–88.1) than CON(44.98,31.3–71) for PCL -Mean ACL volume increased from pre to post-season (pre1426 cc (SD= 288), post 556 cc (SD = 269), p=.006) - Greater volume increase in the right than the left knee (right 211 cc, left 48 cc, p =.047)
Myrick et al.	2019	Observational, prospective	Division-I female collegiate soccer players (n=17)	2013-2014 soccer season	No comparison	
Tendon						
Arampatzis et al.	2007	Interventional non-randomized	Not strength trained adults (n=21, 11 INT, 10 CON)	Isometric plantarflexion (14 weeks)	-Exercise intervention (One leg low strain magnitude and one leg high strain magnitude, INT) -No exercise control (CON) -Plantar flexion contraction+reference protocol leg+ contralateral one legged jumps (G1) -Plantar flexion contraction+reference protocol leg+ contralateral12s isometric plantar flexion (G2) -No specific training (CON)	-Increase in AT CSA at 60% and 70% of tendon length in the high strain leg (p<0.05) -Higher AT CSA at 60% and 70% of tendon length in the high strain leg compared to the low strain leg (p<0.05) -Increase in AT stiffness (p<0.001) in G1 -Increase in AT CSA in G1 reference leg protocol in the 30% to 100% part of the tendon -Increase in the AT CSA in G1 one legged jumps leg in the 20% to 30% part of the tendon -Increase in AT stiffness (p<0.001) in G2 -Increase in AT CSA in G2 both in reference leg protocol and isometric plantar flexion leg in the 30% to 100% part of the tendon
Bohm et al.	2014	RCT	Male adults (n=39, 14 G1, 14 G2, 13 CON)	Plantar flexion exercises (14 weeks)		

Epro et al.	2019	Cross sectional descriptive	Healthy young participants (n= 67, 35 males, 32 females)	No intervention	-High jump (HJ) -Triple jump (TJ) -Long jump (LJ) -Pole vault (PV)	-Greater AT stiffness in the take off leg compared to the swing leg ($p < 0.001$) -Higher AT stiffness in males compared to females ($p < 0.001$) -Lower AT stiffness values in PV compared to HJ ($p = 0.038$), TJ ($p = 0.041$) and LJ ($p = 0.035$) -Higher AT stiffness in INT ($598.2 \pm 141, p = 0.01$) at 14 weeks -Higher AT CSA in INT ($72.0 \pm 11.5, p = 0.007$) at 14 weeks
Epro et al.	2017	Interventional non-randomized	Old female adults (n=34, 21 INT, 13 CON)	Isometric plantar flexion (14 weeks and 1.5 years follow up)	-No exercise control (CON)	-Higher AT stiffness in INT ($637.1 \pm 183, p < 0.001$) at 1.5 years -Higher AT CSA in INT ($71.5 \pm 11, p < 0.01$) at 1.5 years -Higher AT stiffness in the EL group compared to CON (653 ± 187 vs $570 \pm 131, p = 0.048$) irrespective of analyzed leg -Higher AT stiffness in the take off leg compared to the swing leg in the EL group (675 ± 195 vs. $630 \pm 186, p < 0.001$) -Not statistical significant tendencies for greater fluctuation in tendon stiffness in the EL group compared to the CON group at 1 year ($p = 0.074$)
Karamanidis & Epro	2020	Observational cross sectional and longitudinal (1 year and 4 years)	Healthy young participants (n=91, 67 EL, 24 CON)	No intervention	-Elite international level jumping track and field athletes (EL) -Young healthy recreationally active (CON)	
Milgrom et al.	2014	Observational longitudinal	Basic training infantry recruits (n=55)	Basic infantry training (6 months)	No comparison	-Increase in AT CSA in the right leg ($50.2 \pm 9.6, p = .037$) and left leg ($51.1 \pm 8.3, p = .013$)
Werkhausen et al.	2018	Interventional non-randomized	Recreationally active volunteers (n=21, 11 INT, 10 CON)	Explosive isometric unilateral	- No exercise (CON)	-Increase in AT stiffness ($459 \pm 147, p < 0.05$) in the INT group

plantar flexion,
(10 weeks)

Westh et al.	2007	Observational descriptive	Healthy subjects (n=30, 10 MR, 10 FR, 10 NR)	No intervention	-Male runners (MR) -Female runners (FR) -Female non-runners (NR) -Sedentary subjects (SED) -Volleyball players (VOL) -Basketball players (BAS)	-Greater PT CSA in the proximal and distal portion in MR compared to FR and NR (p<0.01) -Greater PT CSA in the mid portion in MR compared to FR (P<0.05) and NR (p<0.01) -Greater distal PT CSA compared to proximal part in MR (p<0.01) and NR (p<0.05) -Smaller AT CSA in the distal part in FR and NR compared to MR (p<0.01)
Zhang et al.	2015	Cross sectional descriptive	Healthy male subjects (n=40, 10 SED, 15 VOL, 15 BAS)	No intervention		-Higher PT CSA in the VOL (dominant leg 127.9 ± 16.2, non-dominant leg 129.4 ± 17.4) and BAS (dominant leg 129.5 ± 32.6, non- dominant leg 133.7 ± 28.3) group compared to SED (p < 0.05)

Muscle

Bickel et al.	2011	Interventional non randomized	Healthy adults (n=70, 31 OLD, 30 YOUNG)	Knee extensor resistance training (16 weeks)	-60-75 year old participants (OLD) -20-35 year old participants (YOUNG)	-Increase in TLM in both OLD and YOUNG (11.164 ± 573 and 13,128 ± 508, p< 0,05) -Increase in Type II fibers CSA in both OLD and YOUNG (4636 ± 298 and 5917 ± 264, p< 0,05) -Increase in Type I fibers CSA in both OLD and Young (5237 ± 241 and 4991 ± 178, p< 0,05)
Fernandez- Gonzalo et al.	2014	Interventional non randomized	Healthy subjects (n=32, 16 men, 16 women)	Bilateral flywheel supine squat resistance	-Men -Women	-Increase total thigh muscle mass in both men (1,031.1 ± 64.4, p<0.05) and women (628.5 ± 50.2, p<0.05)

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Author	Year	Study Design	Population	Intervention	Control	Outcomes
Franchi et al.	2015	RCT	Recreationally active healthy young men (n=10)	Leg press resistance exercise (4 weeks)	-Eccentric leg contraction only (ECC) -Concentric leg contraction only (CON)	-Increased FL in ECC ($5\pm0.6\%$, $p<0.001$) than CON -Increased PA in CON ($7\pm0.9\%$, $p<0.001$) than ECC -Increase in muscle thickness in both ECC and CON ($7.5\pm1.6\%$ and $8.4\pm1.4\%$, $p<0.001$) -Increase in TLM in both ECC and CON ($2.3\pm0.5\%$ and $3\pm0.6\%$, $p<0.01$ and $p<0.001$) -Increase in VL muscle volume in both ECC ($6\pm 0.4\%$, $p<0.0001$) and CON ($8\pm0.5\%$, $p<0.0001$) -Increase in FL in ECC ($12\pm2\%$, $p<0.0001$) compared to CON -Increase in PA in CON ($30\pm0.5\%$, $p<0.0001$) compared to ECC -Difference in VL regional hypertrophy in mid portion between ECC and CON ($7\pm1\%$ and $11\pm1\%$, $p<0.01$) -Difference in VL regional hypertrophy in distal portion between ECC and CON ($+8\pm2\%$ and $+2\pm1.5\%$, $p<0.05$) -Similarities in VL regional hypertrophy in the proximal portion between ECC and CON ($-1\pm1\%$ and $-0.5\pm1\%$)
Franchi et al.	2014	Interventional non randomized	Young men (n=12, 6 ECC, 6 CON) Premenopausal women with FM (n=21, 11 FMT, 10 FMC and 12 CON)	Leg press resistance exercises (10 weeks) Total body resistance training (21 weeks)	-Eccentric exercise (ECC) -Concentric exercise (CON) -Healthy women (CON)	-Increase in CSA in quadriceps femoris in FMT at 5–12/15 femur length ($p<0.05$ – 0.01) -Increase in CSA in quadriceps femoris in CON at 3–12/15 femur length ($p<0.05$ – 0.001)
Häkkinen et al.	2002	RCT				



Holm et al.	2008	Interventional non randomized	Healthy young sedentary men (n=11)	Unilateral resistance training (12 weeks)	-Light load (LL) -Heavy load (HL) -No exercise (CON) -p45: angular velocity 45°/s -p120: angular velocity 120°/s -p210: angular velocity 210°/s -p300: angular velocity 300°/s	-Higher increase in total CSA at quadriceps in HL (7.6±1.4%p<0.05)compared to LL -Increase in FL in all exercise protocols (p45: 5.7%, p= 0.006, p120: 4.2%, p = 0.004, p210: 3.6%, p = 0.024, p300: 7.6%, p = 0.002) compared to CON -Increase in VL volume irrespective of protocol (p< 0.001)
Marzilger et al.	2020	RCT	Young active men (n=47, 33 EX, 14 CON)	Eccentric knee extensor contractions (33 training sessions)		

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