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General

The Effects of Type I Collagen Hydrolysate Supplementation on Bones, Muscles, and Joints: A Systematic Review

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Introduction

Musculoskeletal discomfort is prevalent in primary care, with conditions such as osteoarthritis and osteoporosis being significant contributors. Collagen, particularly type I, is a major structural protein found in connective tissues. The supplementation of type I hydrolyzed collagen has been investigated for its potential benefits in musculoskeletal health.

Objective

This systematic review aims to evaluate the current literature on the effects of type I hydrolyzed collagen supplementation on bones, muscles, and joints.

Methods

A systematic search was conducted in August 2024 using four electronic databases - PubMed, Scopus, EMBASE, and CINAHL. The inclusion criteria were randomized controlled trials (RCTs) and systematic reviews evaluating oral supplementation with type I hydrolyzed collagen. Exclusion criteria were pre-clinical studies, experimental studies, studies not focusing on type I hydrolyzed collagen, studies with beauty-related endpoints, studies that combined collagen with other ingredients, and unblinded, nonrandomized, and uncontrolled trials.

Results

Out of 4,246 articles screened, 36 RCTs met the inclusion criteria. The study protocols varied in population, health conditions, and study duration. Studies focused on bone health faced limitations that prevent definitive conclusions about the effects of collagen supplementation. In contrast, studies on joint health reported beneficial outcomes, such as pain reduction, improvements in clinical parameters, increased physical mobility, and enhanced ankle function. The muscle health studies were inconsistent, with positive effects predominantly observed when supplementation was associated with physical exercise.

Conclusion

Collagen supplementation demonstrates promising results. However, heterogeneity among studies limits the generalizability of findings. Future research should prioritize standardized protocols and consistent outcome measures.

INTRODUCTION

In primary care, the three most common musculoskeletal pain presentations are lower back, knee, and shoulder.[1] Systematic reviews estimate the prevalence of low back pain at 23,2%,[2] knee pain at 22.7%,[3] and shoulder pain at 14.5%.[4] These presentations are often associated with various underlying, especially chronic, conditions. Osteoarthritis (OA) is characterized by the progressive degeneration of articular cartilage, inflicting pain and functional disability. It is estimated that around 250 million people worldwide suffer from OA.[5] Osteoporosis, the most frequent bone disorder globally, results from an imbalanced physiological processes of bone formation and bone reabsorption.[6]

The musculoskeletal system encompasses the bones, tendons, ligaments, muscles, and cartilage, all of which contain an extracellular matrix rich in collagen. Collagen

is a structural protein that confers elasticity and transmits contractile force between fibers.[7,8] Musculoskeletal disorders can be triggered by different factors, such as age, weight, hormonal levels, frequency, and physical activity levels. Populations susceptible to these disorders include individuals over 50 years old,[9] postmenopausal women,[6] overweight individuals,[10] sedentary people,[11] and athletes.[12]

Nutritional interventions, including dietary supplements use, are commonly employed in the management of musculoskeletal disorders.[9] Collagen supplementation may support the treatment as the protein is ubiquitous in connective tissues, consisting of around 30% of human proteins. While there are many types of collagen proteins, type I collagen is the most abundant among them. Type I is primarily synthesized by fibroblasts and osteoblasts and found predominantly in tendons, ligaments, and bones.[7,8] The benefits of collagen intake for conditions that affect the musculoskeletal system have been suggested by previous works.[13-15]

The collagen bioavailability is influenced by the supplement form. Type I collagen hydrolysate is a dietary supplement composed of low molecular weight peptides (<6 kDa) derived from native collagen through heat denaturation and enzymatic hydrolysis.[16,17] This complex multistep hydrolysis results in biologically active collagen peptides that stimulate the metabolism of collagen-producing cells. Collagen peptides or hydrolyzed collagen (HC) offer significant advantages over integral protein forms, such as undenatured collagen, including higher digestibility and absorption rates.[18-20]

Recent collagen reviews have explored the specific effects of collagen supplementation in osteoarthritis, joint injury, and muscle recovery.[13-15] However, no recent reviews have focused on type I collagen hydrolysate. Hence, the study objective is to summarize the literature on the effects of type I collagen hydrolysate supplementation on the musculoskeletal system, specifically regarding bones, muscles, and joints.

METHODS

The searches were conducted in August 2024. The following databases were used: PubMed (MEDLINE), Scopus, EMBASE, and CINAHL. Search strategies were partially constructed using the PICO process (population, intervention, comparison, outcome) and employed terms related to the study's objective, combined with Boolean operators "OR" and "AND". The following terms were used: supplement, oral, nutraceutical, chondroprotec, complement, administration, gelatine, procollagen peptide, collagen, procollagen, 'hydrolyzed collagen', 'collagen hydrolysate', musculoskeletal, muscle, joint, cartilage, ligament, fascia, skeletal, bone. The operator "*" was added to capture variations of terms. In PubMed, search terms were applied in the fields text word, MESH terms, and title. In EMBASE, search terms were applied in the field TITLE-ABS-KEY. Filters for systematic review and randomized controlled trials (RCT) were applied in the respective databases. The search period was from 2000 to August 2024.

Inclusion criteria were RCTs or systematic reviews that investigated oral supplementation of type I collagen hydrolysate, which collagen was administered in isolated form. Exclusion criteria were pre-clinical studies, experimental studies, different types of collagens or non-hydrolyzed collagen, studies combining collagen with other ingredients, studies with beauty-related endpoints, studies not-focused on the musculoskeletal system, and unblinded, nonrandomized, and uncontrolled clinical trials. The search results were added to the Rayyan, a reviewer tool. Duplicate papers and articles without access to full text were excluded. Reviews were included to identify additional studies that might not have been captured by the primary search strategy.

After assessing the eligibility, the studies were grouped according to the main component of the musculoskeletal system the study focused on (bones, joints, and muscles) and the population studied (healthy individuals, patients with osteoarthritis, or individuals with muscle/joint pain).

To obtain an objective metric for the results of the included studies, the Positive Outcome Rate (POR) was applied. The metric was calculated by dividing the number of outcomes with significant improvement (p<0,05) in the intervention group by the total number of outcome measures investigated. A POR value of 1,0 represents the highest possible score, representing an improvement in all studied outcomes.

$$Positive\ outcome\ rate = \frac{Number\ of\ positive\ outcomes\ (p\ <\ 0.05)}{Total\ number\ of\ assessed\ outcomes}$$

RESULTS

The search strategy identified 6042 studies of which 35 RCTs were included in the review. The search workflow is depicted in **Figure 1**. Additionally, four systematic reviews were found and assessed for eligibility. Of these, two studies did not meet the inclusion criteria, one could not be assessed, and one report met the criteria. In total, 36 RCTs were included in the review. Study characteristics are detailed in **Table 1**.

All studies were double-blind, except in two studies: one was only investigator-blinded and the other was participant-blinded. The majority of studies were placebo-controlled, except four that employed parallel groups to evaluate different supplementation doses or protein sources. Four studies utilized crossover designs.

Regarding the sample composition, 16 studies included only male individuals, 7 included only female participants, and 13 studies had mixed-sex samples. In terms of age, 18 studies had participants 18-40 years, nine included participants aged ⩾50 years, and the remaining nine were mixed aged groups. Regarding health conditions, 20 reports included healthy samples while 16 focused on various pathologies.

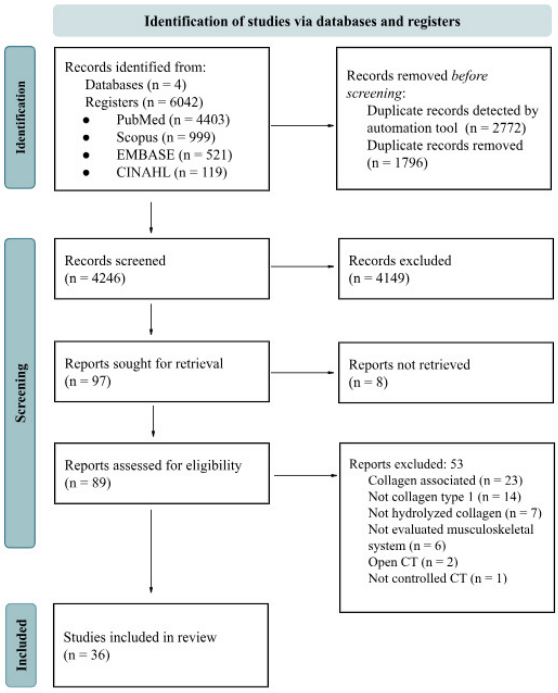

Figure 1. Flow diagram of the searches conducted via databases and registers.

Collagen supplementation doses ranged from less than 5g/day to over 20g/day: 13 studies used 15g/day, eight studies used 10g/day, seven studies used above 20g/day, five studies used 5g/day, and two studies used less than 5g/day. One study did not report the dose. The majority of studies used maltodextrin or silica complex as a placebo, with three reports using whey protein as a comparator.

The average duration of the studies was 15±11.4 weeks, with a maximum duration of 52 weeks (equivalent to one year) and a minimum duration of 0.15 weeks (equivalent to one day). The mean POR of the included studies was 0.4, indicating fewer than half achieved a significant difference in the evaluated outcomes. The average dropout rate was 17.4±10.9 % with an average of 76±57.7 participants per study.

STUDIES FOCUSED ON BONES

Three reports investigated bone-related endpoints. Two studies were on postmenopausal women with osteopenia at a mean age of 60,8 years. One study investigated a healthy male sample at a mean age of 24 years. The supplementation dose varied from 5g/day-20g/day of collagen. The study period ranged from three days to one year. The mean drop-out was 19,9%. The studies used bone formation (osteocalcin (OSCAL), bone-specific alkaline phosphatase (BAP), amino-terminal propeptide of type I collagen (P1NP)) and bone reabsorption (carboxyl-terminal collagen cross-links (CTX), Type I collagen C-telopeptide (CTX 1)) biomarkers to evaluate the endpoints. One study also evaluated bone mineral densitometry (BMD) of the femoral neck and spine between L1 and L4. The endpoints and main results of the studies are summarized in **Table 2**.

Cúneo, F. et al.[6] sought to analyze the performance of bone biomarkers in post-menopausal women with collagen supplementation for 24 weeks. Although BAP and CTX demonstrated differences in their levels during the study period, the difference between groups was not significant. König, et al.[26] designed the study with 5g collagen in a period of one year with a similar sample, also evaluating BMD. P1NP significantly increased in the collagen peptides (CP) group, whereas CTX 1 increased in the placebo group during the period, but the authors did not compare the activity between groups. BMD in the spine and femoral neck had differences between study groups indicating an increase in bone density in the collagen group. However, the groups demonstrated baseline differences for body mass index and BMD spine. Hilkens L, et al.[43] associated collagen supplementation with high-impact exercise in healthy young males. However, both groups demonstrated a difference in bone biomarkers and the study period was three days.

STUDIES FOCUSED ON JOINTS

Fourteen studies assessed the effect of collagen on joints. Of these, two included healthy volunteers, while the remainder focused on individuals with joint pathologies. The pathologies were primarily joint pain, covered in five articles, followed by OA, addressed in five articles, and finally, one study examined participants with chronic knee instability, and one with volunteers suffering from calcaneal tendinitis.

The collagen doses varied between 1,2-20 g/day. Five studies used 5g/day, five used 10g/day, one used 1,2g/day, one used 2,5g/day, one used 8g/day, and one used 20g/day. The trials were conducted between 2011 and 2024, with an average duration of 19,5±10,8 weeks. The total num-

Table 1. Characteristics of the included studies in the review.

Study	Participants	Intervention (Type/Dose)	Period (weeks)	DO (%)
Cúneo, F. et al[6]	82 postmenopausal women with a men age of 57,3 ± 4,8 years and osteopenia	10g/day type I HC	24	13,4
McAlindon, T.E. et al[21]	30 participants aged 49 years or older with mild to moderate knee osteoarthritis.	10g/day COL	48	3,3
Trč, T., Bohmová, J.[22]	100 participants aged 40 years or older with knee osteoarthritis (OA).	10g/day COL	12	7
Bruyère, O. et al[9]	200 participants aged 50 years or older with joint pain.	1,2g/day HC	24	28
Jiang, J.-X. et al[23]	100 women aged between 40-70 years with mild to moderate knee osteoarthritis.	8g/day type I COL	24	6
Zdzieblik, D. et al[24]	60 men >65 years with important muscle strength or physical performance loss in the last 3-4 years	15g/day type I HC + 3-month resistance training	12	11,7
Zdzieblik, D. et al[25]	160 physically active participants aged between 18-30 years with knee joint discomfort related to exercise	5g/day CP	12	13,1
König, D. et al[26]	131 postmenopausal women with a mean age 64,3 ± 7,2 years and osteopenia	5g/day type I CP	52	22,1
Centner, C. et al.[27]	30 healthy men ≥50 years practicing physical activities <60 minutes per week	15g/day HC + low-load training	8	23,1
Clifford, T. et al.[28]	24 physically active men with a mean age of 24,8 ± 4,8 years	20g/day CP + muscle stress induce training	1,29	16,6
Dressler P. et al.[12]	60 athletes with a mean age of 26.9 ± 9.1 years	5g/day CP + mechanical load	24	16,7
Giglio, B.M. et al.[10]	52 overweight women aged between 20-58 years (IMC > 25 kg/m2)	26g/day HC	8	28,8
Jendricke, P. et al.[29]	90 pre-menopause women aged between 18-50 years without previous training	15g/day SCP + resistance training 3x/week	12	14,4
Kirmse, M. et al.[30]	68 healthy physically active men with a mean age of 24 ± 3 years	15g/day SCP + resistance training 3x/week	12	16,2
Oertzen-Hagemann, V. et al[31]	25 male physical education students with a men age of 24.2 ± 2.6 years	15g/day SCP + hypertrophy training 3x/week	12	N/A
Praet, S. et al.[32]	20 participants aged between 36-52 years with tendinopathy	2.5g/day CP + calf resistance training	24	10
Jendricke, P. et al.[33]	90 healthy women aged between 18-40 years and IMC between 18,5-16 kg/m2)	15g/day SCP + resistance training 3x/week	12	34,4
Oikawa, S. et al[34]	11 healthy participants aged between 20-28 years on regular aerobic training	HIIT + CP in 20g after exercise and 40g	1,43	0
Oikawa, S. et al.[35]	22 elderly women aged between 60-80 years	30g/2x a day HC	0,86	0
Bongers, C. et al[36]	200 participants aged between 50-75 years	10g/day COL	12	17
Nunez-Lisboa, M. et al.[37]	9 men aged between 26-40 years	15g/day COL	4	0
Zdzieblik, D. et al[38]	218 physically active participants aged between 18-30 years	5g/day HC	12	17,4
Zdzieblik, D. et al[39]	120 overweight men aged between 30-60 years	15g/day SCP	12	19,1
Centner, C. et al.[40]	30 healthy physically active men aged between 18-29 years	15g/day SCP + high-load resistance training	0,15	0
Jerger, S. et al[41]	40 healthy men aged between 18-40 years	5g/day COL + resistance training	14	32,5
Balshaw, T.	52 healthy men aged between 18-40 years	15g/day CP + resistance training	15	25

et al[42]				
Bischof, K. et al[11]	75 healthy sedentary men aged between 18-40 years	15g/day CP + training	12	26,7
Hilkens, L. et al[43]	17 healthy physically active men with a mean age of 24 ± 4 years	20g/day COL + 3x/day high-load training	0,43	17,6
Jerger, S. et al[44]	50 healthy men aged between 18-40 years	5g/day CP + high-load resistance training	14	38
Kuwaba, K. et al.[45]	20 healthy men aged between 40-65 years	10g/day CP + exercise	12	10
Kviatkovsky, S. et al.[46]	86 physically active participants aged between 40-65 years	10g/day or 20g/day CP	36	31
Thomas, D. et al.[47]	55 recreative athletes aged between 18-55 years with early osteoarthritic changes	COL or COL+exercise	12	9,1
Jerger, S. et al.[48]	50 healthy physically active men aged between 18-40 years	15g/day SCP + training program	12	36
Bischof, K. et al[15]	75 healthy men aged between 18-40 years not exercising more than 3 hours a week	15g/day CP + training	12	27
Devasia, S. et al[49]	115 participants aged between 30-65 years with diagnosis of osteoarthritis and moderate exercise levels	2,5g/day type J COL, 5g/day type J COL, 10g/day type J COL or 10g/day bovine COL	12	7,8
McKendry, J. et al.[50]	45 healthy and nonsmoker men aged between 68-76 years	25g/2x a day COL + Controlled diet	2,14	31,1

DO dropout, *HC* hydrolyzed collagen, *COL* collagen, *CP* collagen peptides, *SCP* specific collagen peptide

Table 2. Outcomes and findings of the studies focused on bone activity.

Study	Outcome measures	Main findings	POR
Cúneo, F. et al[6]	Bone resorption markers (CTX) and bone formation markers (OSCAL and BAP)	(-) No significant difference between the groups.	0
König, D. et al[26]	BMD of the femoral neck and spine (L1-L4), plasma levels of bone markers — P1NP and CTX of type I COL (CTX 1).	(+) ↑ BMD in the spine (p = 0.030) and femoral neck (p = 0.003); ↑ P1NP in the SCP group (p = 0.007).	0,75
Hilkens, L. et al[43]	P1NP and CTX-I markers assessed fasting, and at 24, 48, and 72 hours after COL intake and exercise	(-) No significant difference between the groups.	00

POR Positive Outcome Rate, *COL* collagen, *SCP* specific collagen peptide, *CTX* C-terminal cross-linked telopeptides, *OSCAL* osteocalcin, *BAP* bone-specific alkaline phosphatase, *BMD* Bone Mineral Density, *P1NP* amino-terminal propeptide of type I collagen. ↑ increased, ↓ decreased

ber of participants was 1.652, resulting in an average of 110±71 participants per study with an average dropout rate of 11,3±10,3%.

Outcomes were the most frequently accessed by the Visual Analogue Scale (VAS), cited in 6 articles. Followed by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Knee Injury and Osteoarthritis Outcome Score (KOOS), both of which were used in 3 of the 14 analyzed articles. The rate of positive outcomes in studies examining the effects of collagen on joints was 0.49±0,3. The endpoints and main results of the studies are summarized in **Table 3**.

Zdzieblik et al.[25] observed a POR of 0.6 in the assessment of pain reduction in athletes with functional knee problems during sports activities associated with specific collagen peptides (SCP) use. Pain intensity was assessed using VAS and additional therapies demonstrated a statistically significant improvement in activity-related pain. Bongers et al.[36] reported no superior effect of collagen compared to placebo. Supplementation with both treatments resulted in similar reductions in knee pain and improvements in knee function after 12 weeks.

STUDIES FOCUSED ON MUSCLES

Nineteen articles addressing the collagen effects on muscle strength and body composition. Of these, only one study focused on pathological volunteers. The mean dosage of collagen peptides used was 20g/day. The study durations ranged from less than a day to 15 weeks. The endpoints and main results of the studies are summarized in **Table 4**.

Zdzieblik D et al.[39] investigated the effects of daily supplementation with SCP compared to whey protein and placebo, within the context of a 12-week resistance training program. The study sought to determine whether CP could induce a significant increase in lean mass and a greater reduction in body fat compared to the other groups, especially whey protein. The findings revealed that SCP supplementation, in combination with resistance training, resulted in a significant increase in lean mass and a sub-

Table 3. Outcomes and findings of the studies focused on joint activity.

Study	Outcome measures	Main findings	POR
McAlindon, T.E. et al[21]	RM with Delayed Gadolinium-Enhanced, dGEMRIC (central weight-bearing medial/lateral femoral cartilage, posterior medial/lateral femoral cartilage, and medial and lateral tibial plateau cartilage) and T2 MRI mapping.	(+) ↑ dGEMRIC in the medial (p=0.03) and lateral (p=0.02) tibial regions of interest in the HC group at 24 weeks. T2 cartilage measurements showed little variability or change over time, and no differences between groups in any region.	0,25
Trč, T., Bohmová, J.[22]	VAS and WOMAC	(+) ↑ VAS score for pain in the affected knee (+ p < 0.05); ↑ WOMAC (+ p < 0.05)	1
Bruyère, O. et al[9]	Improvement of >=20% in VAS, Lequesne, DASH, EIFEL, EQ-5D, SF-36	(+) ↑ VAS at T=6 months (p=0.036)	0,17
Jiang, J.-X. et al[23]	WOMAC; Lysholm score; Parameters of liver and kidney function	(+) ↑ WOMAC; ↑ Lysholm score	0,7
Zdzieblik, D. et al[25]	VAS assessed by the physician and participant; Pain intensity at rest; ROM of joint; Use of additional therapeutic options	(+) ↑ VAS in both assessments (p = 0.046; p = 0.021) ↓ additional therapeutic options	0,6
Dressler P. et al.[12]	Cumberland Ankle Instability Tool (CAIT); Foot and Ankle Ability Measure German version (FAAM-G) ADL; FAAM-G Sport and Stiffness-Ankle Arthrometer	(+) ↑ CAIT, FAAM-G ADL and FAAM-G Sport	0,75
Praet, S. et al.[32]	Victorian Institute of Sports Assessment–Achilles (VISA-A), Ultrasound	(+) ↑ VISA-A score	0,5
Zdzieblik, D. et al[38]	Changes in pain intensity (scale from 0 to 100); McMurray test, Steinmann test, and drawer test.	(+) ↓ Pain intensity (p = 0.024) in self-reported pain and also in medical assessment (p = 0.003).	0,25
Thomas, D. et al.[47]	VAS, KOOS, ROM measured with a goniometer, and knee flexor and extensor muscle strength, quantified using a portable dynamometer.	(+) ↑ VAS, strength and KOOS scores. COL supplementation alone did not show superiority in any scenario.	0,4
Bongers, C. et al[36]	VAS, KOOS, Lysholm, inflammatory markers, bone and cartilage formation	(-) Absence of a superior effect of COL. COL and PLA: ↓ knee pain and improvements in knee function after 12 weeks.	0
Jerger, S. et al[41]	CSA of the Achilles tendon, Achilles tendon stiffness, muscle thickness, maximum voluntary torque, dietary intake, and physical activity.	(+) ↑ Achilles tendon CSA (p = 0.002 - +11.0%) compared to the PLA group (+4.7%). ↑ muscle thickness (p = 0.014 +7.3%) compared to the PLA group (+2.7%).	0,5
Jerger, S. et al[44]	Measurement of CSA of the patellar tendon using MRI. B-mode ultrasound of patellar tendon deformation; CSA of the muscle via MRI.	(+) ↑ Patellar tendon cross-sectional area (hypertrophy)	0,25
Kviatkovsky, S. et al.[46]	KOOS, KOOS (gender and exercise frequency), VR-12, VR-12 (gender and exercise frequency)	(+) ↑ All variables but at different times (3, 6, or 9 months) and also with different dosages (10g or 20g).	NM
Devasia, S. et al[49]	WOMAC score, QoL, PICS, serum levels of CTX-II, MOAKS and Pain Scale	(+) ↑ WOMAC, QoL, PICS, CTX-II, and MOAKS (P < 0.05). However, the 10g type had the best outcomes among all arms.	1

POR Positive Outcome Rate, *HC* hydrolyzed collagen, *COL* collagen, *PLA* placebo, *MRI* Magnetic Resonance Imaging, *RM* Cartilage Magnetic Resonance, *dGEMRIC* Magnetic Resonance Imaging of Cartilage, *VAS* Visual analogue scale, *COL* Collagen peptide supplementation, *PLA* Placebo, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index, *QoL* Quality of Life , *PICS* Physician's Impression of Change Score, *MOAKS* MRI Osteoarthritis Knee Score, *KOOS* Knee Injury and Osteoarthritis Outcome Score, *ROM* knee flexion range of motion, *CSA* cross-sectional area, *VR-12* Veterans Rand 12, *EQ-5D* EuroQol 5 Dimension , *SF-36* Short Form-36, *CAIT* Cumberland Ankle Instability Tool, *FAAM-G* Foot and Ankle Ability Measure German version, *VISA-A* Victorian Institute of Sports Assessment–Achilles, ↑ increased, ↓ decreased.

stantial reduction in body fat compared to the placebo. Whey protein supplementation positively impacted lean mass but did not differ from the placebo. There was no significant difference between the effects of CP and whey protein concerning lean mass gains.

Previous research by the same author[24] demonstrated that a 12-week exercise protocol combined with collagen supplementation further improved body composition in elderly, sarcopenic men by increasing lean body mass, muscle strength, and reducing fat mass. Additionally, another study[29] aimed to explore the effects of resistance exercise combined with SCP supplementation on body composition and muscle strength in premenopausal women. The treatment group (TG) exhibited a statistically significant increase in the percentage of lean mass compared to the control group (CG). The women in the study also had a significant decline in overall body fat percentage, with greater body fat loss in the TG.

At the molecular level, Oertzen-Hagemann[31] evaluated the outcomes of a 12-week hypertrophy protocol in men aged from 21-27 years, combined with a daily 15g of SCP supplementation. The objective was to assess the impact of this protocol on muscle proteomics. Although results indicated that the collagen-supplemented group exhibited a more pronounced effect on muscle-related proteins and pathways associated with resistance training adaptation, the findings were not entirely clear. Furthermore, the author found that participants in the intervention group ex-

Table 4. Outcomes and findings of the studies focused on muscle activity.

Study	Outcome measures	Main findings	POR
Zdzieblik, D. et al[24]	FFM, BFM, BM, IQS, and SMC - standardized single-leg stabilization test.	(+) ↑ FFM; ↓ FM; ↑ IQS.	0,6
Centner, C. et al.[27]	Cross-sectional area of thigh muscles (MRI), MIVC, capillary blood: ROS by spectrometer, serum IGF."	(-) No significant difference between the groups.	0
Clifford, T. et al.[28]	Subjective well-being, muscle soreness, a venous blood sample, PTP, CMJ, and MVIC.	(+) ↑ CMJ in 48 hours (P = 0,050).	0,2
Giglio, B.M. et al.[10]	Body composition; Food intake; Biochemical parameters; SF-36	(-) ↑ Android fat.	-0,1
Jendricke, P. et al.[29]	LBM, BFM, MVIC, knee extension, hand grip strength with dynamometry.	(+) ↑ LBM (p<0,05), ↓BFM (p<0,05), ↑ hand grip strength (p<0,05)	0,75
Kirmse, M. et al.[30]	FFM, FM, LC, weight; Muscle thickness via ultrasound; External load (4 parameters); Strength (5 parameters); Resistance RET (MVIC, 1RM, DL, BP, BR); Muscle biopsy (Type I, Type II, Type I fCSA, and Type II fCSA)	(+) ↑ FFM (p<0,001);	0,08
Oertzen-Hagemann, V. et al[31]	Body mass; body fat, lean mass; Strength SQ, DL, BP, and Rowing; MVIC for knee extension.	(+) ↑ Body mass (p=0,035), ↑ LBM (p=0,014), ↑ Strength in rowing (p=0.025); ↑ regulation in the proteome, particularly related to proteins with myofibrillar and extracellular matrix functions	0,375
Jendricke, P. et al.[33]	Running time; Running distance/time; Body composition (BIA); Strength (SQ 1RM)	(+) ↑ Running time (p<0.05), ↑ reduction in heart rate in the running distance test (p<0.01); ↑ LBM, ↑ total body water, and ↑ intracellular water (p<0.05).	0,4
Oikawa, S. et al[34]	Plasma AA: Essential AA, leucine, and tryptophan, tryptophan/large neutral AA ratio (Trp); Muscle protein synthesis through saliva analysis and muscle biopsy.	(-) No significant results in the collagen group	0
Oikawa, S. et al.[35]	Muscle protein synthesis by plasma sample, saliva, and biopsy: 4 criteria: rest and acute exercise, and long-term exercise, respectively	(-) No significant results in the COL group	0
Zdzieblik, D. et al[39]	Lean body mass, isometric strength test, maximum voluntary isometric contraction.	(+) ↑ Lean body mass and ↓ weight loss.	0,4
Nunez-Lisboa, M. et al.[37]	Vertical stiffness and spatiotemporal running parameters.	(-) No significant changes in vertical stiffness or spatiotemporal running parameters in recreational triathletes.	0
Centner, C. et al.[40]	Muscle biopsy - Genetic expression analysis: PI3K-Akt, MAPK, mTOR.	(+) PI3K-Akt and MAPK were significantly upregulated after exercise.	0,6
Balshaw, T. et al[42]	Isometric strength of the knee extensors and flexors; volume of the quadriceps, hamstrings, and gluteus maximus with MRI; evoked contractions, 1RM lifting strength, and quadriceps architecture (with ultrasound)	(+) ↑ Muscle volume in the quadriceps and total value of trained muscles. ↑ Peak torque of evoked contraction.	0,2
Bischof, K. et al[11]	MVC, RFD, peak RFD, CMJ, MS. Body composition, BFM, FFM, BCM, and ECM.	(+) ↑ MVC (p = 0,02), RFD (p < 0,01), Peak RFD (p < 0.01) and CMJ height (p = 0.046).	0,2
Kuwaba, K. et al.[45]	VAS, fatigue, maximum knee extension strength during isometric muscle contraction of both legs, ROM, and blood levels of CPK and LDH.	(+) ↓ VAS of muscle soreness immediately after the exercise load (p < 0.001). ↓ VAS of fatigue immediately after the exercise load (p < 0.001). ↑ muscle strength (p = 0.035).	0,75
Bischof, K. et al[15]	CK, LDH, MYO, and hsCRP to measure post-exercise muscle stress.	(+) MYO (p = 0,017), CK (p = 0,039 and LDH (p = 0,016)	0,75
McKendry, J. et al.[50]	Blood samples and muscle biopsy for measuring integrated myofibrillar protein synthesis, acute anabolic signaling, and metabolic acidosis.	(-) No significant results in the COL group.	0
Jerger, S. et al.[48]	1-hour run assessing heart rate, distance covered, and time. Treadmill running with a constant increase in speed until exhaustion. Blood collection for lactate measurement. Bioimpedance for measuring weight and LBM.	(+) Collagen supplementation demonstrated effectiveness in almost all running and endurance outcomes	0,8

POR Positive Outcome Rate, *COL* collagen, *FFM* Free Fat Mass, *BFM* body fat mass, *BM* Bone mass, *IQS* isokinetic quadriceps strength, *SMC* sensory-motor control, *MIVC* maximal isometric strength, *PTP* pain threshold by pressure, *CMJ* countermovement jump height, *SF-36* Short Form-36, *LBM* Lean body mass, *LC* leg circumference, *1RM* one-repetition maximum, *DL* deadlift, *BP* = bench press, *BR* = bent-over row, *SQ* squat, *PI3K-Akt* phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt), *MAPK* mitogen-activated protein kinase, *mTOR* mammalian target of rapamycin, *MVC* maximal voluntary contraction, RFD rate of force development, *MS* muscle soreness, *BCM* body cell mass, ECM extracellular mass, *ROM* range of motion, *CPK* creatine phosphokinase, *LDH* lactate dehydrogenase, *CK* Creatine kinase, *MYO* myoglobin, *hsCRP* high-sensitivity C-reactive protein, ↑ increased, ↓ decreased.

perienced an increase in body mass and lean body mass, with no significant difference in fat mass between groups.

Jerger and colleagues[44] investigated whether collagen supplementation combined with high-load resistance exercise could upregulate gene expression in pathways involved in skeletal muscle transduction. The study assessed gene expression in the PI3K-Akt, MAPK, and mTOR pathways through mRNA analyses at various time points following exercise. Results demonstrated a significant upregulation of gene expression in the PI3K-Akt and MAPK pathways 4 hours post-exercise in the collagen group. However, there were no significant differences in mTOR pathway expression between the groups. Despite 100% adherence from participants in the study, the evaluation period and sample characteristics limit broader generalization.

DISCUSSION

The purpose of this systematic review was to evaluate the effects of type I HC supplementation on bones, joints, and muscles. Our findings indicate that HC intake might enhance different outcomes in the musculoskeletal components. However, the heterogeneity in study designs, methodological limitations and lack of reporting items, result in an inconsistency of results between studies.

Studies that evaluate bone outcomes were the fewest compared to joints and muscles. All studies presented methodological issues, such as outcomes evaluation, or limitations, such as study period and population sample, that prevent generalizations about the effect of collagen supplementation on bone health. The evaluation of these outcomes in healthy populations is challenging, especially in younger individuals, as the modification of serum biomarkers or BMD is more likely in the occurrence of pathologies. Cúneo, F. et al.[6] and König, D. et al.[26] demonstrated changes in bone biomarker levels in similar populations, postmenopausal women, over different study periods. However, the study groups did not have clear differences, and the modifications mostly occurred despite the collagen intake. The results presented by König, D. et al.[26] indicate that collagen supplementation might assist in the increase of BMD of the femoral neck and lumbar spine in postmenopausal women with osteopenia.

The majority of articles evaluating the effects of collagen supplementation on joint health reported beneficial outcomes, including reductions in joint pain, improvements in clinical parameters,[9] increased physical mobility,[23] and enhanced ankle function[12] (Table 3). Jiang et al,[23] in their study involving women with moderate knee OA, as well as Zdzieblik et al[25,38] in two studies examining the relationship between collagen supplementation and physical exercise, observed significant improvements in joint pain. A hypothesis for the improvement in pain could be the reduction of inflammation. It is suggested that collagen may have anti-inflammatory properties, and supplementation could thus reduce the production of inflammatory markers, thereby improving joint function.[25] The highest number of significant results for HC supplementation in joint outcomes was observed in subjectively reported outcomes[22,23,49] (Table 3). However, the lowest rates of positive outcomes (POR = 0.25) were found in studies that used more objective and precise outcome measures, such as Cartilage Magnetic Resonance Imaging (dGEMRIC), B-mode ultrasound, and specific tests like the McMurray test, Steinmann test, and Drawer test.[21,38,41]

Collagen supplementation is suggested to improve the functional, structural, and contractile aspects of skeletal muscle. Even though our search found studies demonstrating positive effects of collagen supplementation in body composition, the effectiveness of the supplement in increasing muscle mass varies, with some studies demonstrating positive results and others not confirming this effect. Using proteomics, Oikawa et. al.[34,35] showed in two studies that α-lactalbumin and whey were superior to collagen in increasing muscle protein synthesis. In one study, the author showed that myofibrillar and sarcoplasmic proteins, in trained individuals who consumed α-lactalbumin, had superior rates when compared to individuals who consumed collagen peptides, suggesting that a higher protein quality plays a key role in muscle remodeling. Similarly, the same author presented that whey protein had higher protein synthesis rate, corroborating with the anterior result. In addition, Balshaw et al[42] did not find strength gains in subjects who took collagen peptides after a 15-week resistance training protocol. These results reinforce the need for further studies using collagen peptides and their effects on muscle gains.

Our findings are in line with the results found by Khatri et al, 2021.[14] The authors conducted a systematic review about collagen supplementation on body composition, collagen synthesis, and recovery from joint injury and exercise. Improving joint functionality and reducing joint pain were demonstrated as the most beneficial. Changes in body composition, especially in FFM, had improvements when combined with resistance training. Collagen supplementation indicated an increase in collagen synthesis which coupled with an intermittent exercise protocol may improve tissue repair and prevent injuries. Regarding muscle protein synthesis, other high-quality protein sources, such as whey protein, may be more indicated.[14] These findings reinforce the potential of collagen supplementation while acknowledging its limitations compared to other protein sources.

In general, studies presented limitations regarding the duration of the intervention. The mean study period was 15 weeks ranging from 1 day to 1 year (Table 1). Most studies reported significant positive differences after 12 weeks (3 months) or more. Shorter periods of evaluation hardly demonstrated significant differences with only the supplementation use. Certain outcomes due to the physiology of the musculoskeletal system components demand long periods and consistency of intervention to demonstrate substantial differences, such as bone activity.

The studies do not present standardization in dose administration of collagen supplement. The high degree of variability in dosage use impacts the generalization of findings. Additionally, the majority of studies used commercially available collagen supplements without specifying the collagen type. Most reports cited the brand composition

of the collagen, which presents another limitation for generalization as different brands do not have the same amino acid composition even if it is the same type of collagen. The lack of trial design and reporting standardization emerges as obstacles for definitive conclusions regarding the optimal dosage for specific musculoskeletal outcomes.

Most studies had small sample sizes, having 15 studies with a sample size above 50 participants. This feature might generate high variation between studies enabling the occurrence of conflicting findings. The rate of dropouts in the studies cannot be ignored. While a drop-out rate <20% is acceptable, 14 studies reported a rate above the acceptable. Studies with long periods of intervention are more likely to lose participants' adhesion, especially when participants cannot perceive substantial benefits from the intervention.

CONCLUSION

Achieving clinically and statistically significant results is particularly challenging in areas with inconsistent prior research and lack of standardized testing methods, such as evaluating the benefits of collagen as a dietary supplement for joint, muscle, and bone health. Additionally, the multifactorial complexity of these studies and conditions evaluated present another obstacle to drawing definite conclusions regarding the effects of collagen supplementation. Even so collagen supplementation demonstrated positive effects compared to placebo or alternative interventions particularly in high-risk groups, such as elderly adults and individuals with pre-existing joint-disorders, while having a favorable safety profile.

Our review revealed dramatic heterogeneity in study protocols, including differences in sample size, study population, duration, and outcome measurements. The diversity of concentrations and dosages between studies, added to the lack of adverse events (AE) indicate a probable security of collagen supplement. However, it is not clear if patients did not present AEs, or the authors did not report or evaluate.

The dropout rate in several studies exceeded 20%, suggesting that study design or participant adherence may need to be reevaluated. This high rate may have affected sample sizes and compromised the validity of the findings. Additionally, while validated, self-reported outcome measures like VAS may introduce subjectivity. Future research could prioritize more objective assessments, such as MRI, BMD, and ultrasound to enhance the reliability of results.

The relatively short duration of many studies might have contributed to the lower POR, as insufficient time may have prevented substantial physiological changes from being induced. Future research should design study protocols with longer periods of intervention. Furthermore, the commercial funding of most studies raises concerns about potential conflicts of interest. Authors need to clearly state their affiliations, funding and potential conflicts of interest.

Despite these limitations, some studies reported promising results, such as increased BMD, which could have significant implications for clinical practice. Notably, changes in body composition were prominent in studies involving physical exercise and healthy volunteers. Future research should explore whether similar outcomes can be observed in pathological populations, with or without accompanying training protocols. Finally, patients suffering from joint pain could potentially benefit from collagen supplementation if future research provides robust evidence demonstrating its effectiveness in alleviating symptoms.

CONTRIBUTIONS OF EACH AUTHOR

Paula J Brueckheimer, Tales C Silva and Leonardo B Rodrigues: planning, data analysis or interpretation and writing of the article.

Carlos Isaia Filho: conception, planning, critical intellectual review, and responsibility for final approval for publication.

Vivian Zague: critical intellectual review, and responsibility for final approval for publication.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest related to this systematic review. However, it is important to note that one of the authors (VZ) is employed by Genuin, a company that produces hydrolyzed collagen. This affiliation does not influence the findings or conclusions of this review, which are based solely on the analysis of the available literature.

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