The Effect of Collagen Hydrolysate Ingestion in Tendinopathy:

A Randomized Placebo-Controlled trial

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Author: Louis Lepetit Thomsen[1]

Signature and date:  19. Sept 2024

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Co-author: Amanda E. Olsen[1]

Signature and date:  19. Sept 2024

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Senior researcher: Christian Couppé[2]

Signature and date:  20. Sept 2024

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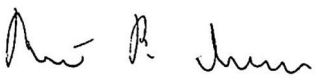
Senior researcher: René B. Svensson[1]

Signature and date:  19. Sept 2024

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Senior researcher: Mette Hansen[3]

Signature and date:  19. Sept 2024

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Other contributors:

Affiliations:

1. Institute of Sports Medicine Copenhagen, Department of Orthopedic Surgery M, Copenhagen University Hospital - Bispebjerg and Frederiksberg and Center for Healthy Aging, Institute of Sports Medicine Copenhagen, University of Copenhagen, Copenhagen, Denmark

2. Department of Physical & Occupational Therapy, Copenhagen University Hospital - Bispebjerg and Frederiksberg

3. Department for Public Health, Aarhus University, Aarhus, Denmark

Resumé

The Statistical Analysis Plan (SAP) outlines the strategy for analyzing data from the randomized, placebo-controlled study on the effect of hydrolyzed collagen ingestion in combination with heavy slow resistance training (HSR) on tendinopathy in male and female elite athletes. This plan includes details on data handling, statistical methodologies, and the interpretation of results.

1. Introduction

The human tendon is comprised primarily of collagen and plays a crucial role in force transmission from muscle to bone, thereby facilitating movement of the human body.[1,2] When the tendon is loaded, force is transmitted to the tenocytes (fibroblast-like cells of the tendon), which respond by secreting various growth factors, which stimulate the production of collagen via autocrine and paracrine signalling.[2,3] Collagen synthesis has been found to be increased by a factor of 2-3 after exercise, peaking after 24 hours.[4,5] However, repetitive sports activity such as jumping and running can lead to tendon overuse injury, so-called tendinopathy. A tendinopathic tendon is characterized by pain during activity, being swollen and tender to palpation, and by reduced performance in sporting activities.[2,6]

Approximately 30% of the world's population will at some time point get a tendon injury, and especially in elite athletes, tendon injuries are a significant problem.[7,8] In elite running and jumping athletes, the incidence[7] and prevalence[9] of tendon injuries are high, and pain symptoms and reductions in tendon function often last several months or even years, impairing elite athlete performance.[8] Moreover, recurrent tendon overuse injury is one of the main causes of career cessation in elite athletes.[5]

Heavy, slow resistance (HSR) training has been shown to be an effective treatment regimen for patellar, Achilles and plantar fascia tendinopathy, both clinically and structurally,[10–12] However, many with lower extremity tendinopathy do not become symptom-free and 20-30% even never respond to loading-based therapy.[10–13]

Ingestion of gelatin and hydrolyzed collagen has been shown to increase the concentration of collagen-associated amino acids (glycine, proline & hydroxyproline) in the blood of human subjects, and if ingested prior to a training bout, a significant increase of collagen synthesis (Procollagen Type 1 N-terminal Propeptide) in the blood, was observed.[14,15] In addition, recently, some studies have shown greater tendon size and mechanics in the lower extremity (in healthy Achilles and Patellar tendons) after ingestion of collagen supplements as an add-on modality to loading-based therapy, compared to placebo.[16,17] Additionally, recent pilot research suggests that ingestion of hydrolyzed collagen protein together with twice daily eccentric-loading (as per Alfredson's protocol) may have a diminishing effect on pain symptoms related to Achilles tendinopathy compared to placebo.[18] However, it has been demonstrated that clinical and structural improvements are similar or even better with HSR only 3 times a week, compared with a twice daily eccentric-loading regimen,[10] but this has not been investigated together with ingestion of a

collagen supplement. It therefore remains unknown whether there is an additive clinical and structural effect of ingestion of a collagen protein supplement, together with a well-structured rehabilitating resistance exercise regimen such as HSR performed 3 times a week, especially in relation to treatment of tendinopathy in elite athletes. Further, it is unknown whether the effect of HSR, with or without collagen supplementation, is sex-specific. In healthy females, tendons have a lower rate of new collagen tissue formation, respond less to mechanical loading, and have different mechanical properties[19–21] This may imply a reduced tendon adaptation response to training and leave the tissue more susceptible to injury. This tendon adaptation response to a rehabilitation resistance exercise regimen for tendinopathy is likely compromised, potentially complicating recovery. However, females only make up a few percent of the participants in scientific trials focusing on tendinopathy.[22,23] This clearly underlines the need for investigating the effect of HSR in both women and men to provide sex specific recommendations for rehabilitation of overused tendons in male and female athletes.

2. Objectives

- Primary Objective: To determine if collagen supplementation combined with HSR reduces tendon pain compared to placebo.

- Secondary Objectives: To assess improvements in tendon structure, function, and overall recovery through various clinical measures, as well as assessing sex differences in the response to collagen ingestion and HSR rehabilitation.

3. Study Design

This is a double-blinded, randomized, placebo-controlled trial with a 12-week intervention period and 26 weeks follow-up.

Potential participants will be screened by phone and then examined at the Institute of Sports Medicine (ISMC) at Bispebjerg Hospital in Copenhagen. This will include a clinical examination and an ultrasound assessment, anthropometric measurements, as well as various questionnaires. If the participant meets the inclusion criteria, they will be offered enrollment and randomized to receive either a collagen supplement (intervention) or a carbohydrate supplement (placebo). Group allocation will be blinded to both participants and investigators, and the supplements will be prepared so they are near-identical in taste and consistency.

Both groups will undergo the same thrice-weekly 12-week training intervention comprised of HSR training. The participants will be required to take their allocated supplement twice daily for the duration of the training intervention. Following the 12 weeks of training, the participants will have a follow-up examination at ISMC.

Six months after the participants finish the intervention, they will be contacted by phone where they will be questioned about their tendon pain.

The initial study design consisted of the analysis of data from 32 male elite athletes. During the course of the project, however, the researchers sought approval from the regional scientific ethics committee to expand the study population to also include 32 female elite athletes. This request was granted, resulting in a total sample size of 64 participants, equally distributed between male and female elite athletes.

Given that the original study design did not account for both sexes, the male and female cohorts effectively represent two distinct randomized controlled trials (RCTs). Consequently, the data analysis will proceed in two phases: first, separate analyses will be conducted for each sex, followed by inter-sex comparisons.

The project has been approved by the regional scientific ethics committee (H-190865531) and is listed as NCT04578418 on clinicaltrials.gov.

See appendix 1 for an overview of the study timeline.

4. Endpoints

- Primary Endpoint: Change in tendon pain assessed by 11-point Numerical Rating Scale (NRS) scores at 12 weeks.

Change in VAS was used as the primary outcome in the original protocol. However, for practical purposes, it was later decided to use an 11-point Numerical Rating Scale (NRS) in the study. The NRS is as sensitive as the VAS, is easier to administer and has a lower failure rate.[24] It has been found to be very strongly correlated with the VAS,[25,26] suggesting that the two can be substituted.

- **Secondary Endpoints:**
  - Changes in Victorian Institute of Sports Assessment (VISA) questionnaire scores.
  - Ultrasonography measurements of tendon thickness and vascularization.
  - Functional tests (single-leg decline squat (SLDS), jump tests).

5. Sample Size Calculation

Based on previous data, a sample size of 14 per subgroup is needed to detect a clinically important difference in VAS scores (<20 points)[27] with a power of 80% and an alpha level of 0.05.

Including a 10% dropout rate, 16 participants per group are required, for a total of 64 participants (32 men and 32 women).

As mentioned above, VAS was used for the original sample size calculation, while an 11-point NRS has been used in the study; however, the results from the two methods are highly correlated.[25,26]

The clinically important difference in NRS has been reported to be 2.0 points in relation to musculoskeletal pain,[27] while the standard deviation has been reported between 1.6 and 2.2.[13,27]

Using 1.9 as an average estimate of the standard deviation yields a sample size of 14 in each group to detect a difference of 2.0 points in NRS with a power of 80% and an alpha level of 0.05, which is comparable to the sample size for the VAS scale.

6. Randomization

Participants will be randomized into two groups (collagen or placebo) using a computer-generated minimization randomization procedure, stratified by type of tendinopathy (patellar, Achilles or plantar fascia) and pain duration (over/under 12 months), and contraception use (women only). Men and women will be randomized separately.

7. Study Methods

7.1. Participants

The inclusion criteria will be as follows:

- Male and female elite athletes
- Age of 18-40 years
- Pain for at least 3 months in either the patella, Achilles or plantar fascia tendon

To be considered an elite athlete, potential participants must have a weekly training volume of at least 10 hours, and be participating in competitive sports, or must have met these requirements immediately prior to their tendon injury.

The exclusion criteria will be as follows:

- Administration of a steroid injection in the tendon within the 3 months leading up to enrollment
- Former surgery in the tendon
- Arthritic disease
- Diabetes
- A confounding diagnosis in relation to the tendon
- Active smoking
- Ongoing pregnancy

If a participant has ingested a collagen product in the period up to enrollment, a 2-week wash-out period will be required.

7.2. Pain and function

The participants' tendon pain will be evaluated at the baseline assessment, during the supervised training sessions, and at the follow-up assessment. Pain will be assessed on an 11-point numerical rating scale (NRS) ranging from 0 to 10, with 0 representing no pain and 10 representing worst imaginable pain. At baseline and follow-up, participants will be asked to perform a tendon-provocation test. Participants with patellar pain will be instructed to do a single-leg decline squat (SLDS) on a 45-degree surface. The participants will perform two squats on each leg: the first squat

will be considered a familiarization, and after the second squat, participants will be asked to evaluate pain in the patellar tendon using the NRS.

Participants with Achilles tendon or plantar fascia pain will be instructed to perform 25 single-leg jumps on each leg. They will be instructed to focus on performing the jumps primarily over the ankle joint to ensure load on the Achilles tendon or plantar fascia. After completing 25 jumps, participants will be asked to evaluate pain in the tendon using the NRS. If a participant fails to complete 25 jumps due to pain, the number of jumps will be noted by the investigator, and pain will be evaluated using the NRS.

Tendon function will be evaluated using the validated VISA-A[28] and VISA-P[29] surveys, as well as the Foot Function Index (FFI). The surveys will be completede at the baseline and 12-weeks follow-up examinations, as well as at the 38-weeks follow-up.

7.3. Ultrasonography

Participants will have an ultrasonographic assessment of their tendon at baseline and follow-up. The scans will be performed on a HI VISION Ascendus (Hitachi Medical Systems) machine by trained investigators.

Tendon vascularity will be evaluated using power Doppler (PD), capturing short video sequences (4-5 seconds). PD scans will be made on an unloaded tendon, with the patient either prone (Achilles) or supine (patella). PD scans will be omitted on participants with plantar fascia tendinopathy, as it has been reported that it is a poor marker for tendinopathy in this tendon.

PD sequences will be imported to Fiji/ImageJ and analyzed using a custom macro to quantify the maximum amount of Doppler activity in a single frame, as described previously.[13] All analyses will be conducted by the same trained investigator and will be made before unblinding.

Anteroposterior (AP) thickness and tendon cross-sectional area (CSA) will be evaluated by capturing stills. AP thickness and CSA measurements of the patellar and Achilles tendon will be made on a tense tendon. For patellar participants, this will be achieved by having the participant sitting on the examination table with a knee angle of 90 degrees. For Achilles participants, this will be achieved by having the participant lying prone, and applying pressure to the forefoot, until the

ankle reaches neutral position. Measurements on the plantar fascia (PF) will be made with the participant lying prone and the knees flexed at 90 degrees, on a relaxed tendon. Only AP measurements will be made on PF participants.

AP and CSA images will be imported to Fiji/ImageJ and analyzed using a custom macro, as used previously.[13] All analyses will be conducted by the same trained investigator and will be made before unblinding.

7.4. Training

For the training-based intervention, a protocol of heavy, slow resistance (HSR) training will be chosen, as it has been shown that it yields comparable clinical results to an eccentric protocol, with a significantly higher degree of satisfaction among study participants.[10,11]

Currently, to the best of the authors' knowledge, no published study has investigated whether the ingestion of a collagen supplement could have an add-on effect to an HSR-training protocol.

The training-based intervention will consist of 12 weeks of HSR training with 3 training bouts per week. One of these bouts will be supervised by a trained investigator. Supervision will be carried out to ensure that the participants perform the exercises with correct technique and tempo, to guide the participants regarding load and tendon pain, and to increase compliance and adherence to the training program. Additionally, the investigator will register whether the participants have taken their supplement correctly during the week.

The participants will be allocated a program consisting of 3 exercises, depending on their afflicted tendon:

1. Participants with patellar tendinopathy will receive a program comprised of back squats, leg extensions and leg press.
2. Participants with Achilles tendinopathy will be asked to perform heel lifts with a barbell on a step-bench, heel lifts in a Smith machine, and heel lifts with the knees 90 degrees flexed.
3. Participants with plantar fascia tendinopathy will perform heel lifts in a Smith machine, heel lifts with a slight flex in the knees performed in a leg press machine, and heel lifts with the knees 90 degrees flexed, with a rolled-up towel under their toes.

Participants will be instructed in the correct tempo of 6-8 seconds per repetition and will be told to have a 2-minute rest between sets and exercises, to ensure adequate recovery.

The per protocol compliance cut-off will be 75% for both the supervised sessions as well as the unsupervised sessions. If a participant has a compliance level below 75%, they will only be included in the intention to treat analysis.

7.5. Nutritional Supplements

After enrollment in the project, participants will be randomized to either the intervention or the control group. Participants in the control group will receive a carbohydrate powder, while participants in the intervention group will receive a mix of hydrolyzed collagen and the carbohydrate powder. The supplements will be mixed in such a way, that they will have nearly identical taste and consistency, to ensure the correct blinding of the participants and researchers. All supplements will be purchased from manufacturers that certify their products are free from banned substances.

Mixing and dosing of the supplements will be carried out by trained, unblinded lab personnel who will never have direct contact with any of the study participants and will not participate in the data analysis.

Participants will be asked to ingest their supplement twice daily – once approximately 60 minutes before exercise and once before bedtime. On days where a participant does not exercise, they will be asked to ingest a portion during the day, and a portion before bedtime. Participants in the intervention group will ingest 5 grams of collagen in each portion, for a total daily intake of 10 grams of collagen.

All participants will also receive 80 mg of vitamin C daily, which is 100% of the recommended daily intake (RDI). Vitamin C is a prerequisite for collagen synthesis,[14,15] so this is to ensure that vitamin C intake will not be a limiting factor in the study.

7.6. Diet registration

Total daily protein intake and low energy intake could be a potential confounding variable affecting tendon collagen synthesis. To account for this, participants will be asked to complete a 3-day dietary record midway through the intervention period. The recording period will consist of two

weekdays and one weekend day, with participants instructed to select a timeframe that best represents their typical dietary patterns, avoiding atypical situations such as fasting, holidays, or other dietary deviations. To ensure consistency across all records, participants will utilize a standardized online dietary tracking software (Madlog, Madlog Aps, Denmark). The investigators will provide participants with an access license for the software.

7.7. 38 Weeks Follow-up

Twenty-six weeks after the intervention (i.e., around 38 weeks after enrollment), the participants will be contacted by telephone to conduct a short interview relating to tendon pain (NRS), perceived group allocation and study satisfaction. Furthermore, PROM questionnaires (VISA & FFI) will be sent to the participants after the phone call.

7.8. Amino acid quantification

To investigate how the blood amino acid profile will be influenced by ingesting a hydrolyzed collagen supplement, a sub-study will be undertaken where 16 of the study participants will be recruited (4 women from the intervention group, 4 men from the intervention group, 4 women from the control group and 4 men from the control group).

They will be asked to arrive at the Institute of Sports Medicine in the morning after an overnight fast. Blood samples will be taken every 30 minutes for 2 hours (t = 0, 30, 60, 90 and 120) for a total of 5 samples. After the first blood sample at t = 0 (control sample), the participants will be instructed to ingest their project supplement.

The samples will be kept at room temperature for 30 minutes, after which they will be kept on ice for at least 5 minutes and until they are centrifuged. Subsequently, the serum fraction will be pipetted into a tube, and the samples will be kept in a freezer at the ISMC until analysis.

The samples will be analyzed at the Department of Biomedical Sciences, Faculty of Health and Medical Sciences at the University of Copenhagen using the method of liquid chromatography-mass spectrometry (LC-MS), as previously reported.[30] In addition, the collagen specific amino acid hydroxyproline will be measured using a colorimetric assay.

8. Statistical Methods

8.1. Data Management

- Data will be stored using REDCap with pseudonymization and encryption.
- Data will be checked for accuracy, missing values, and outliers before analysis.

8.2. Significance level

- A p-value less than 0.05 will be considered significant.
- A p-value less than 0.1 will be considered a trend.

8.3. Baseline Characteristics

- Descriptive statistics (mean, standard deviation, median, interquartile range) will be used to summarize baseline characteristics.
- Differences between groups at baseline will be assessed using t-tests or chi-square tests as appropriate.

8.4. Primary Analysis

Outcomes will be analyzed separately for men and women, except for analyses to specifically compare the two (see below).

- Analysis of the Primary Endpoint:

- A two-way repeated measures ANOVA (time (repeated) x intervention) will be used to analyze pain during sporting activity (NRS scores). The interaction will be the primary outcome, but main effects will be used as secondary outcomes. The sexes will be analyzed separately for the primary outcome.
- If data do not meet ANOVA assumptions, appropriate non-parametric tests (e.g., Friedman test) will be used.

8.5. Secondary Analysis

The following secondary outcomes will be analyzed with a two-way repeated measures ANOVA:

- VISA-A, VISA-P and FFI-scores (both total score and truncated form).[31,32]

- Ultrasonographic Measurements (power doppler and tendon thickness).
- Functional Tests (single-leg decline squats and one-leg jumps)
- Pain after primary sporting activity, pain at rest, pain in the morning and maximum pain within the last week (NRS scores).
- Weekly pain (NRS score), Likert-scale and training volume.

The following secondary outcome will be analyzed with an unpaired t-test.

- The percent change in NRS compared between sexes within each group.
- The percent change in tendon thickness compared between sexes at the group level.
- The delta value in power doppler compared between sexes at the group level.
- The average intake of energy (kJ/day), protein (g/day, g/day/kg and % of daily energy intake (E%)), carbohydrate (g/day and E%), fat (g/day and E%), within each group. Before analysis, the Goldberg cut-off limits will be applied to exclude dietary records that show clear signs of under-reporting.[33]

8.5. Handling of Missing Data

- Intention-to-treat (ITT) principle will be applied.
- Missing data will be handled using repeated measures ANOVA in SigmaPlot (Grafiti LLC, Palo Alto, CA, USA).

9. Sensitivity Analysis

- Sensitivity analyses will be conducted to test the robustness of the results, including per-protocol analyses and analyses excluding participants with protocol deviations.

10. Interim Analysis

- No interim analyses are planned.

11. Software

- All statistical analyses will be conducted using SigmaPlot (Grafiti LLC, Palo Alto, CA, USA).

12. Reporting

- Results will be reported following the CONSORT guidelines.
- All findings, including negative and inconclusive results, will be published to ensure transparency.

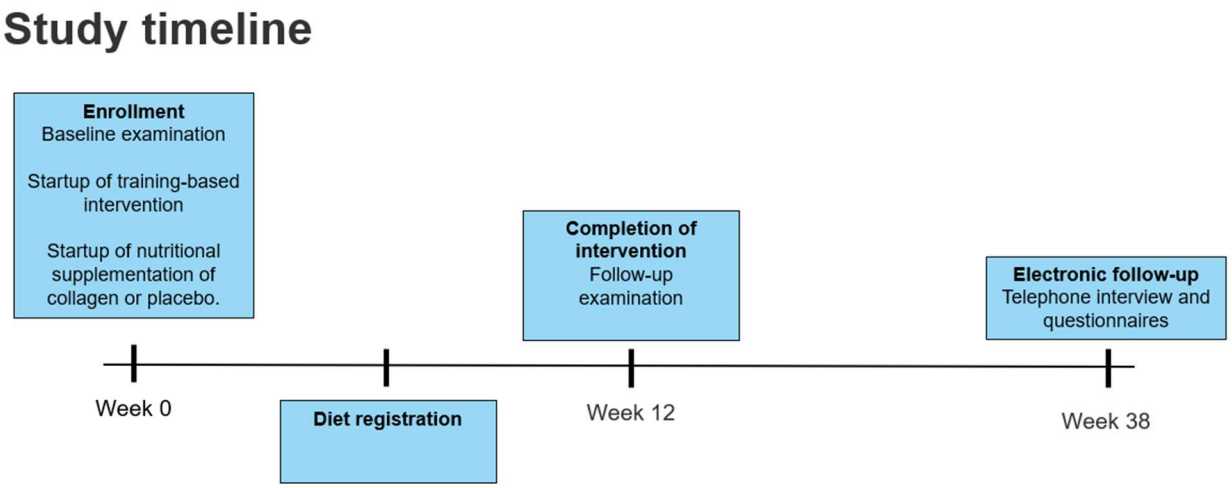
13. Ethical Considerations

- The study will adhere to the ethical guidelines outlined in the protocol and approved by relevant ethics committees.

14. Conclusion

This SAP provides a comprehensive plan for analyzing data from the study on the effect of collagen hydrolysate ingestion in tendinopathy. Following this plan will ensure the reliability and validity of the study findings.

Appendix 1


Study timeline
Enrollment
Baseline examination
Startup of training-based intervention
Startup of nutritional supplementation of collagen or placebo.
Completion of intervention
Follow-up examination
Electronic follow-up
Telephone interview and questionnaires
Week 0
Diet registration
Week 12
Week 38

References

1. Millar, N. L. *et al.* Tendinopathy. *Nat Rev Dis Primers* **7**, 1 (2021).
2. Magnusson, S. P. & Kjaer, M. The impact of loading, unloading, ageing and injury on the human tendon. *J Physiol* **597**, 1283–1298 (2018).
3. Kjaer, M., Jorgensen, N. R., Heinemeier, K. & Magnusson, S. P. Exercise and Regulation of Bone and Collagen Tissue Biology. *Prog Mol Biol Transl Sci* **135**, 259–291 (2015).
4. Miller, B. F. *et al.* Coordinated collagen and muscle protein synthesis in human patella tendon and quadriceps muscle after exercise. *J Physiol* **567**, 1021–1033 (2005).
5. Magnusson, S. P., Langberg, H. & Kjaer, M. The pathogenesis of tendinopathy: balancing the response to loading. *Nat Rev Rheumatol* **6**, 262–268 (2010).
6. Khan, K. & Cook, J. The painful nonruptured tendon: Clinical aspects. *Clinics in Sports Medicine* vol. 22 711–725 Preprint at https://doi.org/10.1016/S0278-5919(03)00035-8 (2003).
7. Kujala, U. M., Sarna, S. & Kaprio, J. Cumulative Incidence of Achilles Tendon Rupture and Tendinopathy in Male Former Elite Athletes. *Clin J Sport Med* 133–135 (2005).
8. Lopes, A. D., Junior, L. C. H., Yeung, S. S. & Costa, L. O. P. What are the Main Running-Related Musculoskeletal Injuries? *Sports Med* 891–905 (2012).
9. Lian, O. B., Engebretsen, L. & Bahr, R. Prevalence of jumper's knee among elite athletes from different sports: a cross-sectional study. *Am J Sports Med* **33**, 561–567 (2005).
10. Kongsgaard, M. *et al.* Corticosteroid injections, eccentric decline squat training and heavy slow resistance training in patellar tendinopathy. *Scand J Med Sci Sports* **19**, 790–802 (2009).
11. Beyer, R. *et al.* Heavy Slow Resistance Versus Eccentric Training as Treatment for Achilles Tendinopathy: A Randomized Controlled Trial. *Am J Sports Med* **43**, 1704–1711 (2015).
12. Rathleff, M. S. *et al.* High-load strength training improves outcome in patients with plantar fasciitis: A randomized controlled trial with 12-month follow-up. *Scand J Med Sci Sports* **25**, e292-300 (2015).
13. Agergaard, A.-S. *et al.* Clinical Outcomes, Structure, and Function Improve With Both Heavy and Moderate Loads in the Treatment of Patellar Tendinopathy: A Randomized Clinical Trial. *Am J Sports Med* **49**, 982–993 (2021).
14. Shaw, G., Lee-Barthel, A., Ross, M. L., Wang, B. & Baar, K. Vitamin C-enriched gelatin supplementation before intermittent activity augments collagen synthesis. *Am J Clin Nutr* **105**, 136–143 (2017).
15. Lis, D. M. & Baar, K. Effects of Different Vitamin C-Enriched Collagen Derivatives on Collagen Synthesis. *Int J Sport Nutr Exerc Metab* **29**, 526–531 (2019).
16. Jerger, S. *et al.* Effects of specific collagen peptide supplementation combined with resistance training on Achilles tendon properties. *Scand J Med Sci Sports* **32**, 1131–1141 (2022).
17. Jerger, S. *et al.* Specific collagen peptides increase adaptions of patellar tendon morphology following 14-weeks of high-load resistance training: A randomized-controlled trial. *Eur J Sport Sci* **23**, 2329–2339 (2023).

18. Praet, S. F. E. *et al.* Oral Supplementation of Specific Collagen Peptides Combined with Calf-Strengthening Exercises Enhances Function and Reduces Pain in Achilles Tendinopathy Patients. *Nutrients* **11**, (2019).
19. Miller, B. F. *et al.* Tendon collagen synthesis at rest and after exercise in women. *J Appl Physiol (1985)* **102**, 541–546 (2007).
20. Magnusson, S. P. *et al.* The adaptability of tendon to loading differs in men and women. *Int J Exp Pathol* **88**, 237–240 (2007).
21. McMahon, G. & Cook, J. Female Tendons are from Venus and Male Tendons are from Mars, But Does it Matter for Tendon Health? *Sports Med* (2024) doi:10.1007/s40279-024-02056-7.
22. Schuppisser, M. V., Mondini Trissino da Lodi, C., Albanese, J., Candrian, C. & Filardo, G. Achilles tendinopathy research has a gender data gap: A systematic review and meta-analysis. *Knee Surgery, Sports Traumatology, Arthroscopy* (2024) doi:10.1002/ksa.12046.
23. Mondini Trissino da Lodi, C., Landini, M. P., Asunis, E. & Filardo, G. Women Have Tendons… and Tendinopathy: Gender Bias is a "Gender Void" in Sports Medicine with a Lack of Women Data on Patellar Tendinopathy—A Systematic Review. *Sports Medicine - Open* vol. 8 Preprint at https://doi.org/10.1186/s40798-022-00455-6 (2022).
24. Williamson, A. & Hoggart, B. Pain: A review of three commonly used pain rating scales. *Journal of Clinical Nursing* vol. 14 798–804 Preprint at https://doi.org/10.1111/j.1365-2702.2005.01121.x (2005).
25. Bijur, P. E., Latimer, C. T. & Gallagher, E. J. Validation of a Verbally Administered Numerical Rating Scale of Acute Pain for Use in the Emergency Department. *Academic Emergency Medicine* **10**, 390–392 (2003).
26. Deloach, L. J., Higgins, M. S., Caplan, A. B. & Stiff, J. L. *The Visual Analog Scale in the Immediate Postoperative Period: Lntrasubject Variability and Correlation with a Numeric Scale*. http://journals.lww.com/anesthesia-analgesia.
27. Salaffi, F., Stancati, A., Silvestri, C. A., Ciapetti, A. & Grassi, W. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. *Eur J Pain* **8**, 283–291 (2004).
28. J M Robinson C Purdam P J Visentini J Ross N MaVulli J E Taunton K M Khan, J. L. C. The VISA-A questionnaire: a valid and reliable index of the clinical severity of Achilles tendinopathy. *Br J Sports Med* 335–341 (2001).
29. Visentini, P. J. *et al.* The VISA Score: An Index of Severity of Symptoms in Patients with Jumper's Knee (Patellar Tendinosis). *Journal of Science and Medicin in Sport* 22–28 (1998).
30. Elmelund, E. *et al.* Opposing effects of chronic glucagon receptor agonism and antagonism on amino acids, hepatic gene expression, and alpha cells. *iScience* **25**, (2022).
31. Comins, J. *et al.* Assessment of content validity and psychometric properties of VISA-A for Achilles tendinopathy. *PLoS One* **16**, (2021).
32. Agergaard, A. S. *et al.* Assessment of the Psychometric Properties of the Danish VISA-P. *Transl Sports Med* **2023**, (2023).

33. Goldberg, G. R. *et al.* Critical evaluation of energy intake data using fundamental principles of energy physiology: 1. Derivation of cut-off limits to identify under-recording. *Eur J Clin Nutr* **45**, 569—581 (1991).