

Article

Oral supplementation of specific collagen peptides accelerates improvement in Achilles tendon pain and function in combination with a tailored exercise intervention

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Abstract: The current pilot study investigates whether oral supplementation of specific collagen peptides improves symptoms and tendon vascularisation in patients with chronic mid-portion Achilles tendinopathy in combination with structured exercise. Participants with chronic mid-portion Achilles tendinopathy were randomized to 3 months of bi-daily doses of 2.5g specific collagen peptides or a placebo 30 mins before exercise. Group AB received specific collagen peptides for the first 3 months before crossing over to placebo. Group BA received placebo first before crossing over to **specific collagen peptides**. All participants followed a bi-daily calf strengthening program and milestone-based return-to-running program for 6 months. At baseline, 3 and 6 months, VISA-A questionnaires and microvascularity measurements through contrast-enhanced ultrasound were obtained in 20 patients. Linear mixed modeling statistics showed that after 3 months, VISA-A increased significantly for group AB with 12.6[9.7;15.5], while in group BA VISA-A increased only by 5.3[2.3;8.3] points. After crossing over group AB and BA showed subsequently a significant increase in **VISA-A** of respectively 5.9[2.8;9.0] and 17.7[14.6;20.7]. No adverse events were reported. Microvascularity decreased in both groups to a similar extent and was moderately associated with VISA-A ($R^2:0.68$). We conclude that oral supplementation of specific collagen peptides may accelerate the clinical benefits of a well-structured calf strengthening and return-to-running program in Achilles tendinopathy patients.

Keywords (MESH): Achilles tendon; microvessels; contrast-enhanced ultrasound; hydrolysed collagen supplementation

1. Introduction

The treatment of chronic Achilles tendinopathy remains challenging with a relatively high percentage of non-responders. There are many proposed treatment options, of which an eccentric exercise program is currently the first treatment of choice. Despite the good results on pain scores after eccentric exercises, a 5 year follow-up study showed that only ~40% of the patients were completely pain free and 48% had received one or more alternative treatments.^[1] In accordance,

there is still a need for treatments that would improve the benefits of a structured eccentric exercise program. Recent studies indicate that both cardiometabolic[2,3], as well as nutritional factors[4,5] can modulate local tendon healing. Although clinical studies are still scarce, a recent IOC consensus statement on dietary supplements in high-performance athletes[6] proposes that dietary supplementation containing gelatin or hydrolysed collagen could potentially be useful for athletic populations as increased intake of collagen-derived peptides has been shown to modulate collagen synthesis[7] and improve tendon-[8] and joint-related pain.[9,10] Others have shown that glycine, as the most abundant component of collagen hydrolysates[11], has disease modifying properties in both animal[12,13] and *in vitro*[14] models of **tendinopathy**. We therefore aimed to study the potential clinical benefits of a specific porcine-derived hydrolysed collagen supplement as add-on therapy to 6 months of an eccentric calf strengthening and well-structured return-to-running program. Furthermore, to improve our understanding of the *in vivo* working mechanism of a hydrolysed collagen supplement on tendon **vascularisation**, we also aimed to investigate microvascular changes of the Achilles tendon using real-time contrast-enhanced ultrasonography (CEUS)[15]. In a recently published study[16], it was shown that CEUS provides a more objective and reproducible assessment of tendon microvascularity in comparison with power Doppler ultrasound. Furthermore, CEUS was also shown to be moderately associated with increased Achilles tendon symptoms. We hypothesized that improvements in tendon pain and function throughout the course of the intervention would be reflected by a reduction in CEUS-based tendon microvascularity. A previous ultrasonographic tissue characterisation study has shown that structural integrity is decreased in both Achilles tendons in people with unilateral Achilles tendinopathy.[17] As dietary supplementation of hydrolysed collagen appears to have systemic effects on collagen-dense tissue[11,18], we aimed to study both tendons of each individual patient, independent of whether participants had uni- or bilateral symptoms.

2. Methods

The current study is a prospective double-blinded placebo-controlled clinical trial with a cross-over design. Through balanced within block-randomization (computer-based, 5 individuals per block), eligible participants were allocated to each study arm by an independent staff member to either 3 months **of twice daily 2.5 g hydrolysed** specific collagen peptide (sCP) (TENDOFORTE®, GELITA AG) or a placebo product to be dissolved in water, both pre-packed in identical sachets. The placebo sachets contained 2.5g of maltodextrin (CARGILL) obtained by enzymatic conversion of starch. The sachets containing sCPs or placebo were absolutely identical in appearance and the products were equal in flavor and texture. After 3 months participants who received the sCPs were crossed-over to the placebo product (group AB) and vice versa (group BA). Allocation concealment was further ascertained by allocating an individual to group AB or group BA. No patient, research nurse, assessor or any other medical or research staff was aware of the treatment assignments for the duration of the study. All data and statistical analyses were also completed before the randomization code was broken at the end of the completed trial.[19] Based on lack of previous data sets that allowed for a power analysis and sample size calculation, we designed a small-scale pilot study with multiple outcome measures that involved 2 groups of 10 participants. Data collection of this single-center trial was performed in an outpatient sports medicine clinic of a national high-performance sports institute. Study design was approved by the local ethics committee of the Australian Institute of Sport and prospectively registered (ANZCTR#12615001035516). Patients were not involved in our study design. Participants were recruited by social media and advertisements. In- and exclusion criteria are summarized in **Appendix A**.

2.1. Exercise intervention

In addition to the nutritional intervention, all participants followed a well-structured eccentric calf strengthening program and milestone-based return-to-running program for a total duration of 6 months. The eccentric exercise started with a calf raise using the unaffected limb (or both limbs if

the symptoms were bilateral), followed by an eccentric drop using the injured leg. The exercise was performed with both the knee straight and the knee bent to target the gastrocnemius and soleus muscles respectively. Over 26 weeks participants were instructed to perform 2 x 90 repetitions daily, despite the presence of pain.[20] All participants were instructed to avoid weight-bearing sporting activities for the first four weeks. When participants reported less than 2 out of 10 pain on single leg hopping, they were allowed to start with low-intensity running exercises. Details and milestones used within this program can be found in Appendix B. Half an hour before the calf strengthening exercises, participants were instructed to ingest 2.5g of sCP or placebo product dissolved in a glass of cold water. This provides sufficient time for orally ingested sCPs to be absorbed in the gut and appear in the blood stream.[21] Participants kept a diary of their calf strengthening exercises and were asked to return any leftover sachets at both their 3 and 6 months follow-up appointments.

2.2. Outcome Measurements

All participants underwent a series of measurements and evaluations at baseline, 3 and 6 months to evaluate their response to the combined exercise and nutritional intervention. All measurements and questionnaires were scheduled within a time frame of 3 days and performed by the same team of health practitioners and researchers who were blinded for the nutritional intervention and trained in the standardized operating procedures for the different measurements.

2.3. VISA-A questionnaire, Patient satisfaction and Return-to-Running

One day prior to the ultrasound examinations, all patients were asked to rate their subjective Achilles tendon pain and functional limitations for both the right and left Achilles tendon separately using a Victorian Institute of Sports Assessment–Achilles (VISA-A) questionnaire[22]. After 3 and 6 months patients also received a questionnaire to rate their satisfaction and to what level they had been able to resume their running sports activities (Appendix C).

2.4. Real-time harmonic contrast enhanced ultrasound (CEUS) measurements

Contrast-enhanced ultrasound (CEUS) measurements scans were performed as described in previous studies. [15] [16] Patients were prone with fully extended knees and both ankles immobilized with an ankle angle between 5-10 degrees plantar flexion whilst ensuring minimal tendon tension. Both Achilles tendons were examined in the longitudinal plane with a 58 mm long high-frequency (5–14 MHz) linear array transducer (model 14L5/PLT-1005BT) on an Aplio™500 (TUS-A500, Toshiba/CANON Medical Systems). The transducer was longitudinally positioned in the Achilles tendon midline using a retort clamp attached to the bed. A 12G copper wire was placed between transducer, gel and skin to locate and mark tendon insertion in a reproducible manner. Tendon insertion was defined as the attachment point of most ventral tendon fibres to the calcaneal bone. A total of seven skin marks at 1-cm intervals were used to position the ultrasound probe over the tendon mid-portion (2–6 cm). Probe pressure was kept to a minimum to avoid blood vessel obliteration. Scanning parameters were optimised for 3 cm depth and kept constant for all participants. Real-time harmonic contrast-enhanced ultrasound (CEUS) of the Achilles tendon mid-portion was performed through the injection of 10uL.kg⁻¹ body weight bolus of agitated contrast agent (DEFINITY™, Lantheus Medical Imaging) in a forearm vein, followed by 10 ml 0.9% saline solution. CEUS is based on second harmonic imaging of intravascular circulating microbubbles with a diameter of ~1-3 micron. These microbubbles act as echo-enhancers and are used with the aim to identify small vessels (down to 40 micron).[23] Participants were instructed not to talk or change body position during recordings. Blood pressure and heart rate were measured every 5 min throughout the procedure with a digital sphygmamometer and automatically inflating arm cuff (OMRON HEM-7130). As peak flow of CEUS signal was achieved within 2 minutes following the bolus injection, only first 120 sec of digital CEUS data were used for further analysis. To allow for complete washout of perflutren gas through the lungs, a minimum of 15 min was allowed between consecutive CEUS measurements of right and left Achilles tendon. Dedicated contrast harmonic

image quantification software (2B771-005EN*V, Toshiba/CANON Medical Systems) was used for time-curve analysis (TCA). In the present study, it involved the examination of a 25x13 mm region of interest (ROI) that included at least 2 mm of the anterior fat pad. Within this ROI, the relative microvascularity (MV) values were determined as peak log-scaled signal intensity in decibels (dB) of a normalised smoothed curve during the first 2 min after subtraction of baseline signal intensity 20-25 sec after bolus injection. Inter-observer reliability for CEUS-based MV-values was previously shown to be excellent with an ICC of 0.97. [15] [16]

2.5. Blood sampling

At baseline, non-fasting blood samples were obtained from venipuncture to determine total cholesterol, triglycerides and uric acid and exclude (familial) hypercholesterolaemia[24] and gout[25] as a contributing factor to tendinopathy.

2.6. Product safety and Monitoring of Adverse events

Specific collagen peptides are characterized by a considerably high safety profile. So far no clinical indications of allergies have been observed. No incompatibilities with other diets or medications have ever been described in the medical literature. Collagen peptides received the GRAS status from the Food and Drug Administration. "GRAS" is an official abbreviation which stands for "generally recognized as safe." (<https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/SCOGS/ucm261307.htm>) Nevertheless, participants were instructed to report any gastro-intestinal or other side effects that they thought were potentially associated with the intake of the investigational product or placebo.

2.7. Statistical analyses

All data are presented as means $\pm$ SD. Baseline values of all parameters were tested for uniformity via discriminant analysis. All data processing and statistical analyses were performed before de-blinding the randomization order. Linear mixed model (LMM) analysis using R statistical software package was used to determine the association between CEUS-based microvascularity values and VISA-A scores at the 3 different time points. For statistically significant interactions, we determined R^2 , which represents the variance explained by the combination of fixed effects and random effects. ANOVA was used for all other comparisons. LMM analysis was also performed to test for changes in our main outcome variables between examination at baseline and following the 3 and 6 months intervention periods between and within groups in a cross-over design. The LMM analysis satisfies all conditions of an intention-to-treat analysis and has also been shown to be the most powerful statistical method under a variety of conditions that are common to randomized controlled trials.[26] Carry-over effects within our cross-over design were accounted for in our LMM-analyses by looking at interaction of the order and treatment effect across time. A p value <0.05 was considered statistically significant.

3. Results

3.1. Study population

From September 2015 until April 2016, a total of 60 patients (32 men/28 women, age 43 $\pm$ 10 yrs) with subjective Achilles tendon symptoms showed interest in our study. Following initial screening, 40 potential candidates (18 men/22 women, age 43 $\pm$ 11 yrs) were excluded or withdrew for the following reasons: not meeting age criteria (n=3), current lack of symptoms (n=1), logistical challenges (n=13), a recent Achilles tendon rehabilitation program or injection therapy (n=2), insertional Achilles tendinopathy (n=1), partial Achilles tendon rupture (n=2), safety concerns (n=1), unknown/not interested anymore (n=17). A total of 20 patients (13 men/7 women, age: 44 $\pm$ 8 yrs, BMI: 24.4 $\pm$ 3.3 kg.m⁻²) with clinical symptoms (mean duration 54 $\pm$ 90 months) of uni- (n=7) or bilateral (n=13) mid-portion Achilles tendinopathy were formally included in the study following a

detailed medical history and physical examination by a sport and exercise physician (Figure 1). Demographic characteristics and blood test results of participants at baseline are presented in Table 1. To evaluate homogeneity of the data at baseline between the 2 groups a discriminant analysis was carried out. The data revealed no statistically significant differences between both study groups. All participants wished to return to pain-free running and had either uni- or bilateral Achilles tendon tenderness on palpation. The clinical diagnosis was based on the presence of tenderness and/or tendon thickening 2 to 6 cm proximal to the distal insertion. One asymptomatic tendon that previously had undergone surgery for a complete Achilles tendon rupture was excluded from our analysis.

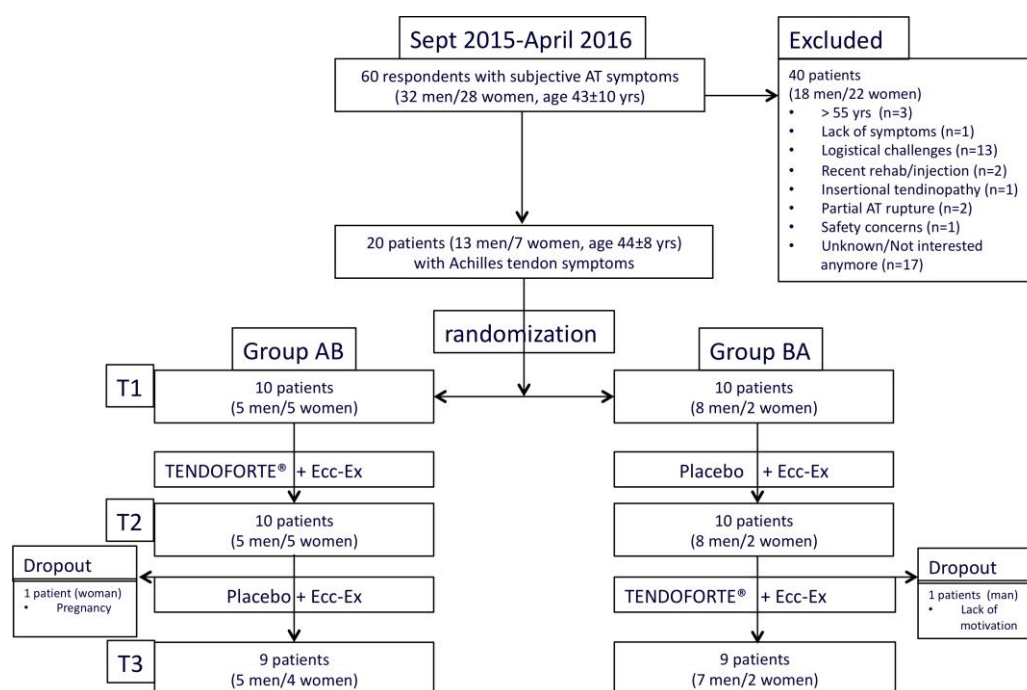


Figure 1. CONSORT Study Flow diagram.

Table 1. Baseline-characteristics study population (n = 20).

	Group AB	Group BA	Total
Total	10	10	20
Male Female	5 5	8 2	13 7
Age (yrs)*	45.3 ± 6.4	42.0 ± 9.4	43.7 ± 8.0
BMI (kg.m ⁻²)*	23.4 ± 3.23	25.5 ± 3.3	24.4 ± 3.3
Total Cholesterol (mmol.L ⁻¹)	5.6 ± 0.7	5.2 ± 0.8	5.4 ± 0.8
Triglycerides (mmol.L ⁻¹)	1.9 ± 2.1	1.7 ± 1.1	1.8 ± 1.7
Urate (mmol.L ⁻¹)	0.3 ± 0.1	0.4 ± 0.1	0.4 ± 0.1
Symptom duration (months) &#	24 (0-180)	18 (0-360)	24 (0-360)
VISA-A symptomatic tendons*	58.5 ± 19.9 (n=17)	55.9 ± 21.9 (n=15)	57.6 ± 20.3 (n=32)
VISA-A asymptomatic tendons*	77.0 ± 18.4 (n=3)	88.5 ± 10.3 (n=4)	84.7 ± 12.9 (n=7)

* mean ± std dev, &median, min-max, # all tendons, based on pooled data of both symptomatic and asymptomatic tendons.

3.2. Change in VISA-A scores

Changes in Achilles tendon pain and function scores during the treatment were evaluated through the Victorian Institute of Sports Assessment–Achilles (VISA-A) questionnaire[22]. Baseline VISA-A scores from right and left limb were not significantly correlated (Pearson’s R: 0.39 [95%CI: -0.08; 0.72], p=0.097). VISA-A score for the group AB at T1 was on average 60.8 (95%CI: [52.0-69.6]), similar to the group BA at T1 (62.8, 95%CI: [54.0-71.6]). Linear mixed modeling statistics showed

that after 3 months, estimated mean difference in VISA-A score for group AB was 12.6 (95%CI:[9.7-15.5]) points, while in group BA this was 5.3 (95%CI [2.3;8.3]) points (Figure 2). After crossing over the AB and BA group showed an estimated mean difference in VISA-A score of respectively 5.9 (95%CI [2.8-9.0]) and 17.7 (95%CI [14.6-20.7]) between T2 and T3. Both group AB and BA achieved the same estimated mean improvement in VISA-A score between T1 and T3 of respectively 18.5 (95%CI: [15.5-21.6]) and 23.0 (95%CI: [19.9-26.1]) (Figure 2). Importantly, our LMM analyses showed that there was a statistically significant interaction from our randomization ((LMM, $F(2,762)=20.3$, $p<0.0001$)) on change in VISA-A scores indicating a significant difference between the groups in evolution of the VISA-A scores over time in relation to sCP versus placebo supplementation.

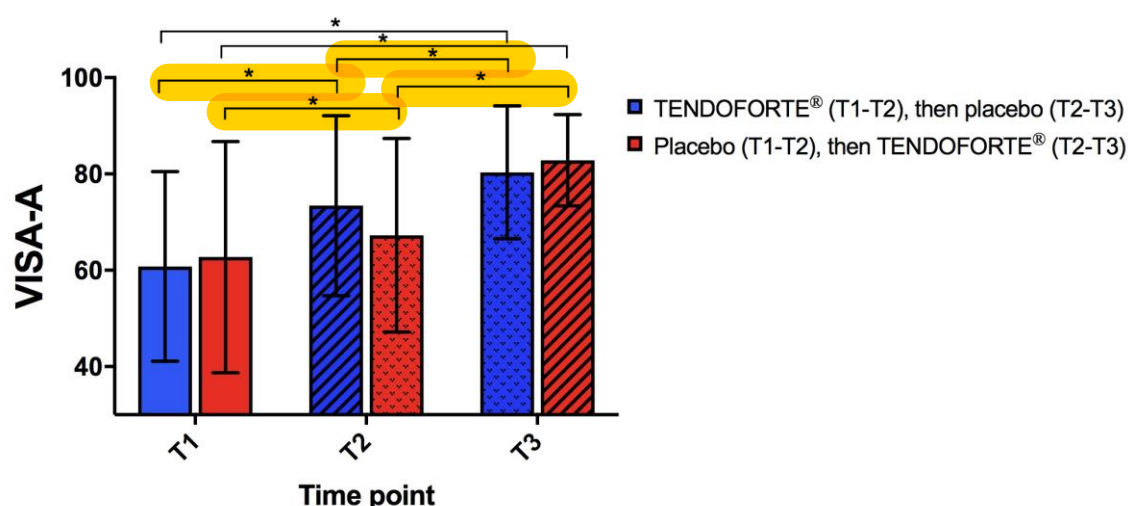


Figure 2. Progression of the mean VISA-A scores during the course of the study Data represent mean±SD. Statistical analysis of changes in VISA-A scores at T1, T2 and T3 via linear mixed modeling. P values ≤ 0.05 were considered statistically significant and marked with an asterisk.

3.3. Patient Satisfaction and Return-to-running Sports

After 3 months respectively 6 out of 10 participants in group AB and 7 out of 10 participants in group BA reported their treatment as ‘good or excellent’. After 6 months 7 out of 9 participants in group AB and 7 out of 9 in group BA reported to be satisfied with their treatment. The success of the intervention is also reflected in Figure 3, summarizing the number of participants that were able to return to their desired (running) sport, although none of them was able to return to their pre-injury level within the duration of the study.

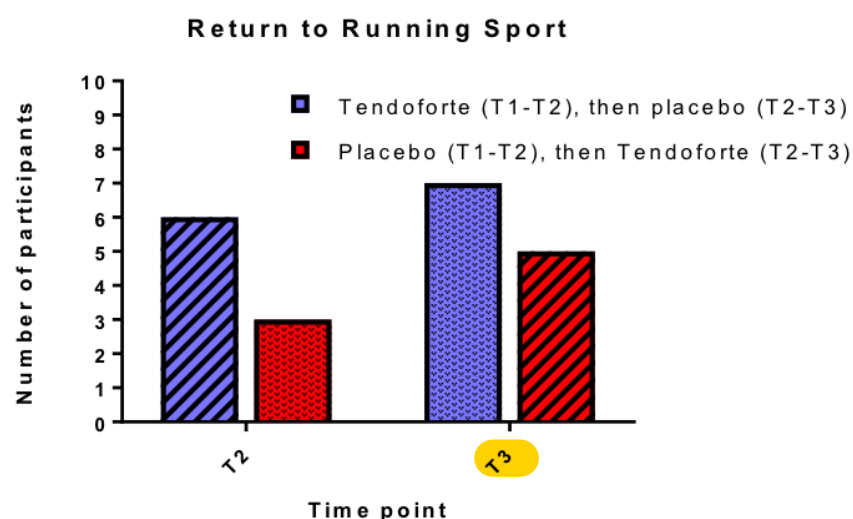


Figure 3. Number of participants that was able to return to their running sport at T2 and T3. Due to low numbers: Chi-square statistics were not possible on these data.

3.4. Change in Achilles tendon microvasculature

Both group AB and BA showed a significant (LMM, $F(2,202)=12.8$, $p<0.001$) decrease in tendon microvasculature over the course of the intervention as assessed by CEUS. As is illustrated in Figure 4, there is no difference in effect between the 2 interventions and no evidence for a benefit of sCP supplementation on tendon vascularisation. The difference at T2 for the 2 different randomisation groups is only marginally significant (LMM, $F(2,202)=2.81$, $p=0.062$), due to the greater variability in the group AB compared to the BA group, in particular on that time point. Our LMM analyses indicate a significant interaction between microvasculature and VISA-A symptom score over the course of the study ($R^2: 0.68$; LMM, $F(2,196)=3.32$, $p=0.038$).

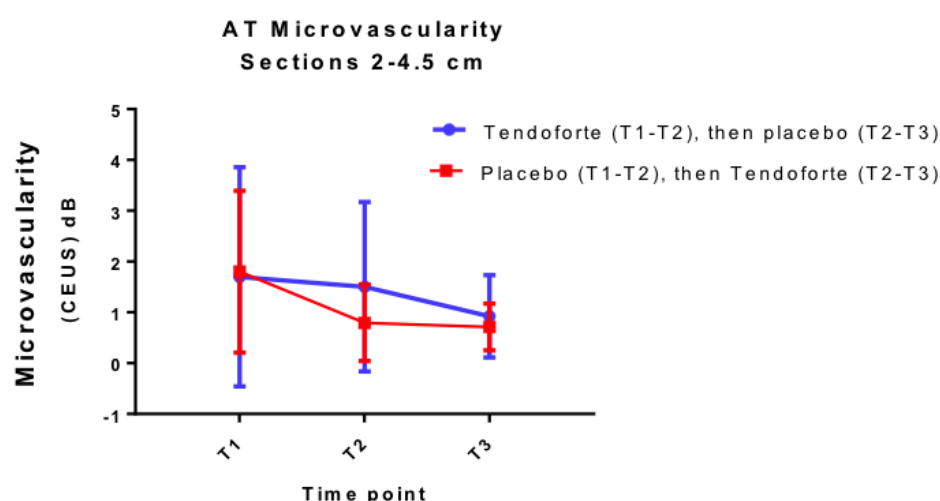


Fig 4. Changes in microvasculature of the Achilles tendon mid-portion (2-4.5 cm from insertion) over time (both symptomatic and asymptomatic tendons combined);.

3.5. Compliance to interventions and adverse events

In group AB, no compliance data on the daily calf strengthening exercise were available for 1 participant at both T1-T2 and T2-T3. In group BA, compliance data on the daily calf strengthening exercise were missing for 1 participant (T1-T2), 1 participant (T2-T3), and 1 participant ((T1-T2 & T2-T3). Based on the available exercise diaries both groups AB and BA showed and achieved a similar compliance of respectively $84\pm11\%$ and $78\pm14\%$ ($P=0.326$) to the twice-daily calf strengthening exercises over the 6 months intervention period.

In group AB, no compliance data regarding intake of investigational product were available for 1 participant at both T1-T2 and T2-T3. In group BA, compliance data were missing for 3 participants (T1-T2) and 1 participant (T2-T3). Compliance to intake of sCPs and/or placebo was respectively $89\pm15\%$ and $91\pm9\%$ ($P=0.906$) for group AB and BA over the 6 months intervention period. At T2, 6 out of 10 in group AB and 4 out of 10 in group BA correctly guessed their allocation to active or placebo supplement. At T3, 4 out of 9 in group AB and 5 out of 9 in group BA correctly guessed their allocation to active or placebo supplement. A total of 1 participant in group BA reported minor gastro-intestinal discomfort after ingestion of the investigational product during the first week of the treatment whilst using placebo. Following a medical check-up with an independent physician who was debinded for the randomization order of this participant, it was decided that there was no clear association with the dietary intervention and this participant was advised to continue with the trial. After 1 week, a medical follow-up learned that all gastro-intestinal symptoms had disappeared. Except for mild delayed onset muscle soreness of the calf muscles in response to the eccentric exercise, no other adverse events were reported during the course of the intervention.

4. Discussion

The main finding of this small-scale but well-controlled pilot study is that oral supplementation of sCPs with high glycine content may accelerate the clinical benefits of a well-structured calf strengthening and return-to-running program in patients with uni- or bilateral chronic Achilles tendinopathy symptoms. Although the study was not powered to detect differences in VISA-A scores or return-to-running sport activities between the 2 groups, it is interesting to note that, independent of randomization order, both clinical outcome variables appear to improve more during the sCPs supplementation period. Although the differences between the 2 groups at 3 months may appear small, the mean change in VISA-A score in group AB of 12.6 [9.7;15.5] points is well above the minimum clinically important difference (MCID) of 6.5 for Achilles tendinopathy patients.[27] In our placebo group BA, VISA-A increased only by 5.3 [2.3;8.3] points after 3 months, which is below the MCID of 6.5. After crossing over from sCP to placebo and vice versa, group AB and BA showed an opposite response with subsequently a significant increase in VISA-A of respectively 5.9[2.8;9.0] and 17.7[14.6;20.7]. These clinical findings extend on two earlier studies[28,29], that reported respectively a pain modulating and *in vitro* anti-inflammatory effect of a nutraceutical containing collagen, mucopolysaccharides and vitamin C. Furthermore, in a rodent model of collagenase-induced Achilles tendinopathy, a 5% glycine rich diet for 3 weeks improved hydroxyproline, glycosaminoglycans and non-collagenous protein content of the Achilles tendon.[12] Glycine has also been shown to improve collagen matrix organisation strength and tenocyte remodelling, most likely by modulating both TNF-alpha, matrix metalloproteases and the availability of collagen precursors.[14] As the sCP supplement in the present study contains 22% of glycine[10], it could be postulated that the increased intake of 1.1 g of glycine per day may have contributed to observed clinical improvements in VISA-A scores during sCP supplementation. Due to nature of the co-intervention, a true washout period to bring participants back to their baseline condition is in Achilles tendinopathy patients not possible. From a pharmacokinetic perspective, the serum hydroxyproline content following the ingestion of hydrolysed collagen peptides returns to baseline within 12 hrs.[21] Nevertheless, any potential carry-over effects have been accounted for in our LMM-analyses by looking at interaction of the order and treatment effect across time.

Given the small scale of the study and unequal distribution of men and women in our 2 study groups, there is a potential of selection bias. Although the adaptability of tendon to loading differs in men and women[30], we are not aware of any intervention study that specifically showed clinically relevant gender difference in VISA-A scores following a calf strengthening program. To evaluate homogeneity of the data at baseline between the 2 groups a discriminant analysis was carried out. The data revealed no statistically significant differences between both study groups. Unfortunately, the relatively low number of female participants do not allow for a gender-based inference.

A strength of the present study is that there were only 2 dropouts after T2, 1 in each group, which is a negligible number. Given that our LMM approach operates on a missing at-random-assumption, we deemed the reasons for dropout not violating the assumptions of the model. Furthermore, attrition is low and no individuals were excluded from our LMM so the possibility of selection bias is considered low in the present study. Nevertheless, as the clinical improvements in VISA-A scores after 3 months are in the same range as previously published studies on eccentric calf strengthening programs[31], no firm conclusions can be drawn regarding the added benefits of sCP supplementation in chronic Achilles tendinopathy. So, although the present randomized controlled and double-blinded crossover study found a **significant interaction of sCP supplementation on change in VISA-A score during a 6 months calf strengthening plus structured return-to-running program**, our findings require duplication in a larger and adequately powered clinical trial.

From a clinical perspective, it is important to note that the majority of our participants had a relatively long history of mid-portion Achilles tendinopathy not responding to rest or other physiotherapy regimes. The latter is also reflected by the fact that placebo group BA only showed a clinically relevant improvement in VISA-A score after they were switched over to sCPs

supplementation. This cross-over effect indicates that sCPs supplementation could be a useful adjunct therapy in Achilles tendinopathy patients whom are not responding to a well-standardized eccentric calf strengthening exercise program.

To improve our understanding of the *in vivo* working mechanism of specific collagen peptides, we also investigated the microvascular changes of the Achilles tendon using a novel medical imaging technique based on contrast-enhanced ultrasonography. The present study is the first of its kinds showing that objectively quantified Achilles tendon microvascularity is inversely and moderately associated with Achilles tendon symptoms throughout the course of a therapeutic intervention. The latter indicates that CEUS of tendons may be a useful and more objective medical imaging technique to monitor the clinical response to a therapeutic intervention. Although a previous publication showed that CEUS has a better sensitivity in detecting microvascular abnormalities as compared to power Doppler ultrasound[16], the observed change in CEUS-based microvascularity during the course of the intervention was not associated with the intake of specific collagen peptides. Our rather large inter-subject variability in Achilles tendon microvascularity at baseline may have precluded detecting any statistically significant differences between the 2 groups. Nevertheless, our results are well in line with several other PDU-based imaging studies that reported rather equivocal responses in microvascularity following conservative treatment of Achilles tendinopathy.[32-36] Despite the longitudinally observed association between CEUS-based microvascularity and Achilles tendon symptoms, it is unlikely that CEUS will be useful in determining the potential *in vivo* working mechanism of specific collagen peptides as an adjunct treatment to a well-structured eccentric calf strengthening exercise program.

5. Conclusion

Although this pilot study has limited statistical power and requires duplication in a larger clinical trial, oral supplementation of sCPs may accelerate the clinical benefits of a well-structured calf strengthening and return-to-running program in patients with chronic Achilles tendinopathy symptoms. Further imaging studies are required to understand the potential *in vivo* therapeutic working mechanism of sCPs within tendons.

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