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Research Article

The effect of intact vs hydrolysed collagen on recovery from exercise induced muscle damage: A double-blind, randomised, placebo-controlled trial

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ABSTRACT

Collagen supplementation has the potential to aid in the recovery from exercise-induced muscle damage (EIMD). A novel collagen supplement, rich in intact type I collagen (Natiiv™, Trinsic Collagen Limited), potentially increases delivery of its constituent amino acids and intact alpha helices to the extracellular matrix (ECM) for remodelling. Thirty-six healthy, young and active adults (M = 27, age: 21.3 ± 4.3 years, body mass index; 25.2 ± 5.7 kg m^{-2}) were assigned (1:1:1) in a double-blind, randomised, placebo-controlled trial, to consume either: Natiiv™ collagen (0.255 g·day^{-1} of Natiiv™ collagen), hydrolysed collagen (20 g·day^{-1} of collagen; Peptan®, Rousselot, Belgium), or placebo (collagen depleted alkaline water; Natiiv™), for 30-days. On day-28, muscle damage-inducing exercise (150 drop jumps) was undertaken. Exercise performance (counter movement, squat, and drop jumps), quadriceps strength (maximal voluntary isometric contraction; leg pain (visual analogue scale, pain pressure threshold, short recovery and stress scale questionnaire); and knee inflammation (via colour fraction ultrasonography) and systemic inflammation (IL-6, IL-10, TNFα); ECM damage (hydroxyproline) and; bone turnover (β-CTX and P1NP) were assessed at baseline, 2.5-h, 24-h, 48-h and 72-h following EIMD. Thirty days of Natiiv™ collagen supplementation had no significant effect on any outcome measure ($P > 0.05$ with small-medium effect sizes) compared to hydrolysed collagen or placebo. Future studies should explore the potential efficacy of Natiiv™ collagen supplementation in other relevant populations/scenarios and assess the post-prandial bioavailability of Natiiv™ collagen and, if impaired, explore interventions that can increase its bioavailability and optimise recovery from EIMD.

1. Introduction

Exercise involving eccentric muscle extensions (i.e., lengthening), and/or unaccustomed exercise, causes damage to skeletal muscle and the extracellular matrix (ECM), referred to as exercise-induced muscle damage (EIMD) (Stožer et al., 2020). The extent of the EIMD is related to the starting length of the muscle (Child et al., 1998; Nosaka & Sakamoto, 2001), force (Nosaka & Sakamoto, 2001) and velocity (Chapman et al., 2006). During exercise EIMD damage manifests in multiple ways including, muscle fibre degradation (Mackey & Kjaer, 2017), increased intramuscular proteins (e.g., hydroxyproline (Tofas et al., 2008)) in peripheral plasma circulation (Hyldahl & Hubal, 2014), swelling (Zainuddin et al., 2005); and a reduced range of motion (Chen et al., 2011). There is also some evidence of contractile protein

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dysregulation/ultrastructural damage (i.e., Z-line streaming) (Shepstone et al., 2005) although the data here are equivocal (Yu et al., 2002). Together, these deleterious effects lead to a delayed onset muscle soreness (DOMS) (Hotfiel et al., 2018), impaired muscle function (Raastad et al., 2010), an impaired ability to perform activities of daily living (Dannecker & Koltyn, 2014), and suboptimal exercise performance (Byrne et al., 2004).

Collagen, a structural protein particularly rich within connective tissue (e.g., cartilage, tendon), skin and bone, is the most highly abundant protein in the body, representing the primary structural protein within the ECM (Bendall, 1967; Dransfield, 1977), with fibrillar types I and III being the most prevalent in skeletal muscle (Bailey et al., 1979). The ECM is comprised of multiple components including collagen proteins, integrins, glycoproteins and proteoglycans (Gillies & Lieber, 2011). Collagen is considered an 'incomplete' protein devoid of the essential amino acid tryptophan, however, it is particularly rich in glycine and proline which can act as precursors supporting increased muscle connective protein synthesis rates, during the post-exercise period (Aussieker et al., 2024). Indeed, whilst glycine and proline are non-essential amino acids, it has been speculated that higher 'quality' protein (e.g., dairy) ingestion may not provide sufficient glycine and proline. This is important as, by extension, connective tissues are also rich in these amino acids (Eastoe, 1955). In support of this notion, whilst muscle collagen synthesis rates do not seem to be nutritionally sensitive at rest (Babraj et al., 2005; Mittendorfer et al., 2005), the ECM is highly sensitive to mechanical loading such as eccentric exercise (Gillies & Lieber, 2011) and, there is accumulating evidence of extensive remodelling of muscle and tendon collagen following EIMD (Han et al., 1999; Miller et al., 2005).

There is growing interest in the possibility that oral supplementation of collagen may enhance collagen synthesis in muscle and bone in vivo, specifically with hydrolysed collagen (Shaw et al., 2017). Briefly, protein hydrolysates are produced by chemically unfolding proteins and enzymatically hydrolysing the peptide bonds at various points in its primary structure, to produce varying quantities of shorter chain peptides and free amino acids (Thomson & Buckley, 2011). Treating collagen protein this way results in 'pre-digestion', which has been suggested to facilitate subsequent amino acid bioavailability and absorption (Morgan & Breen, 2021; Thomson & Buckley, 2011). However, new products may offer alternative routes to increase collagen peptides in the circulation. Natiiv™ collagen is a triple helix collagen molecule that consists of 3 strands of amino acids; glycine-X-Y, where X and Y are frequently proline or hydroxyproline (Persikov et al., 2003; Ramshaw et al., 1998). Natiiv™ collagen is rich in fibrillar type I collagen, is water soluble and unique such that the triple helix is recovered intact, separated (embargoed patented solutions) into strands (specifically type1; α1 and α2), as opposed to the hydrolysed form. Consequently, this theoretically increases delivery of its constituent amino acids to the ECM. However, the effect of Natiiv™ collagen on recovery from EIMD has not been empirically investigated. Theoretically, if delivery of collagen peptides (and its constituent amino acids) to the ECM can be increased, then it may enhance recovery of EIMD.

Therefore, the aim of this novel double-blind, randomised, placebo-controlled trial was to assess the effects of oral Natiiv™ collagen supplementation at its commercially available dose following EIMD on exercise performance, strength, inflammation, and bone turnover compared to a hydrolysed collagen peptide and placebo. We hypothesised that 30-days of Natiiv™ collagen supplementation prior and briefly after EIMD would improve: 1) recovery of exercise performance; 2) recovery of strength; 3) reduce pain; and reduce markers of 4) inflammation; 5) ECM damage and; increase biomarkers of 6) bone turnover, when compared with a hydrolysed collagen peptide supplement and placebo.

2. Methods

This double-blind, randomised, parallel, placebo-controlled trial was granted a favourable ethics opinion by the Faculty of Science and Health Ethics Committee (SHFEC 2023-010) at the University of Portsmouth, and pre-registered on the Open Science Framework (OSF.IO/8DUZF" title = "https://doi.org/10.17605/OSF.IO/8DUZF">https://doi.org/10.17605/OSF.IO/8DUZF) in adherence to the declaration of Helsinki.

2.1. Participants

Forty young healthy adults were recruited via word of mouth and provided fully informed written consent prior to participation. All participants were engaged with sport at a minimum of British Universities and College Sports, or the equivalent, and excluded if they were currently using anti-inflammatory medications, or were contraindicated to exercise. Participants were randomised (1:1:1) using sealedenvelope.com via a concealed allocation to one of three conditions (Natiiv™; hydrolysed collagen, or placebo) with minimisation to each group based on both their baseline quadriceps maximal voluntary contraction (MVIC) strength, as well as their sex. The primary outcome was counter movement jumps (CMJ) presented in centimetres (cm), derived from the measured impulse which were recorded on force plates. Differences were tested for between supplements (main effect of supplement type). An *a priori* sample size calculation suggested that, for 81 % power and an alpha of 0.05, with an effect size estimated ~0.55 (Clifford et al., 2019), 36 participants (12 per group) were required to detect a change in CMJ at 72-h post-EIMD. In total, 40 participants were therefore required, accounting for 10 % attrition.

2.2. Experimental design

Participants were instructed to attend the laboratory on 6 occasions, over 31-days. Upon recruitment and completion of consent, a standard medical history was obtained along with anthropometric data (stature and body mass) and an average of three blood pressure measurements recorded following 15 min of supine rest. Female participants were asked to complete a menstrual cycle questionnaire to determine menstrual cycle phase; with all testing scheduled to occur during the early/mid luteal phase if not on contraceptive medication (Keane et al., 2015; Romero-Parra et al., 2021). Thereafter, a familiarisation session for all movement tests which initialled a minimum of 3 repetitions and a maximum of 5 of each task. This was deemed appropriate given the athletic status of our cohort. Baseline testing were performed for: exercise performance via CMJ, squat [SJ], and drop jumps [DJ]; quadriceps strength via maximal voluntary isometric contraction [MVIC]; pain via visual analogue scale and short recovery and stress scale [SRSS] questionnaire; and synovial (via colour fraction ultrasonography) and systemic inflammation, ECM damage and bone turnover (via biochemistry) prior to day 1 of supplementation to assess outcomes without the potential effects of the supplementation. Following 28-days supplementation, participants arrived at the laboratory to complete the muscle damage protocol (see section 2.3). Following an initial assessment, 2.5 h after muscle damaging exercise, participants returned to the laboratory 24-h, 48-h, and 72-h post-exercise to repeat the below measures to assess recovery from exercise. On each occasion, participants were asked to arrive at the laboratory in a rested and fully hydrated state, having avoided caffeine and alcohol for 3-h and 24-h, respectively. Participants were also asked to replicate (unmonitored) diet and avoid strenuous exercise for 48-h and 24-h respectively, prior to each testing session and arrive after a night of habitual sleep. Participants were instructed not to use of anti-inflammatory medication and/or icing, which was verbally confirmed or denied at each visit and subsequently recorded on clinical record folders where necessary.

2.3. Experimental protocol

Following the pre-experimental baseline visit, participants were randomly assigned to consume 300 ml/day of commercially available Natiiv™ collagen (Natiiv; containing 0.255 g·day^{-1} of Natiiv™ collagen, Trinsic Collagen Limited, UK), hydrolysed collagen (hydrolysed collagen; containing 20 g·day^{-1} of collagen; Peptan®, Rousselot, Belgium (100 % type 1 collagen, 90 % bioavailability after 4 h)) or a non-protein placebo (collagen-depleted alkaline water; Natiiv™) for 30-days. Daily doses were arbitrarily separated into two, with one consumed at breakfast and the second with an evening meal. Natiiv™ collagen and the placebo were indistinguishable in colour, texture, appearance, and odour. Each supplement was consumed with 50 mL of Ribena™ light cordial and water per day. Following 28-days supplementation, participants visited the laboratory to perform the muscle damage protocol (150 drop jumps). Briefly, participants were instructed to jump from a 60 cm box and land on two feet, squat to ~90° knee flexion, then vertical jump with a maximal effort. This was repeated 150 times. Jumps were performed in 6 sets of 25, with 2-min rest between sets. This protocol has previously been shown to induce significant muscle damage (~20 % reduction in MVIC) in a young healthy population (Clifford et al., 2019). Participants were instructed to refrain from strenuous physical activity for the 72-h following the intensive exercise protocol and continue supplementation for 48-h after the EIMD session (i.e., a total of 30 days). At each visit, 24-h diet recall used to verify a similar diet between experimental visits.

2.4. Outcome measures

2.4.1. Jump performance

CMJ, SJ, and DJ were performed to assess muscle power and stretch shortening cycle function (Suchomel et al., 2016; Jarvis et al., 2022). Participants completed three trials of each jump in a randomised order (randomizer.org), on two portable force plates (1000 Hz; Hawkin Dynamics., ME, USA). CMJs involved participants descending into a squat to a self-selected depth before immediately jumping vertically and maximally. SJs required participants to descend into a squat at approximately 90° knee flexion and hold this position for 3-s before jumping vertically maximally ensuring no descending movement was completed after the pause. DJs required participants required to step off a 35 cm box (resulting in a 30 cm drop) and perform a maximal vertical jump upon landing whilst being instructed to minimise ground contact time and maximise jump height. A visual demonstration and familiarisation trials were performed prior to testing to ensure all participants were comfortable with each movement. Force data were processed using the Hawkins Dynamics HD Software (https://www.mdpi.com/1424-8220/October 23, 4820). Eccentric utilisation ratio (EUR) was calculated, as the ratio between CMJ and SJ height (McGuigan et al., 2006). Modified reactive strength index (mRSI) during the CMJ and DJ was calculated by dividing jump height by the movement time (Ebben & Petushek, 2010), with the onset of movement determined as described by Owen, Watkins (Owen et al., 2014), and ground contact time, respectively.

2.5. Quadriceps strength

Quadriceps strength was measured as the maximal knee extensor torque produced during an isometric contraction, using an isokinetic dynamometer (HUMAC NORM; Computer Sports Medicine inc., Stoughton, MA). Following a self-selected warm up, participants were positioned on the dynamometer, the axis of rotation of their dominant knee was aligned to the dynamometer lever arm, and knee angle set to 60° flexion (Thorstensson et al., 1976). Repetition duration was set to 4-s and inter-repetition rest to 45-s. Two familiarisation sets (45-s apart) were followed by three testing trials where instructions were provided for the participant to extend their leg as forcefully as possible for the full 4-s. The average torque from the best set was used for further analysis.

2.6. Synovial inflammation

Synovial inflammation was assessed in the right knee of each participant using ultrasound (Terasson, MA, USA) and vascular software. Specifically, two-dimensional colour doppler images of the suprapatellar recess of the knee were captured, both longitudinally and transversally, with participants supine with their knees at 20° flexion supported by a pillow (Kasukawa et al., 2007). The region of interest was identified by landmarking the quadriceps tendon, femur, and patella. Doppler settings were standardised, and the gain function was limited to reduce artefact noise in the data. Images were cropped (longitudinal scans: 35 × 17 mm and transverse scans: 33 × 23 mm; horizontal length × vertical length) and transferred to MatLab (Boston, MA, USA) for identification of colour pixels. Care was taken to avoid vascular blood flow pixels (Fukae et al., 2010). Colour fraction was calculated as the total number of colour pixels vs. grey scale pixels and combined for longitudinal and transverse scans (Terslev et al., 2003). All scans were performed by one individual with significant experience using ultrasonography. The region of interest were verified by multiple academics during the piloting phase.

2.7. Leg muscle pain and DOMS

DOMS was measured by a 100 mm visual analogue scale (VAS) at rest. Participants were asked to indicate, via a vertical mark, the degree of DOMS they feel on the VAS scale where 0 mm = no pain and 100 mm = unbearable pain (Hjermstad et al., 2011). The mark was then measured and recorded. The Short Recovery and Stress Scale (SRSS) questionnaire (Perkins et al., 2022) comprises of 8 questions. Participants responded to each question on a 7-point Likert scale in relation to their highest known state, with responses ranging from 0 (does not apply at all) to 6 (fully applies). The SRSS asks participants to subjectively rate the following dimensions of their stress and recovery state (refereed to a recovery capability): Physical Performance Capability; Mental Performance Capability; Emotional Balance; Overall Recovery; Muscular Stress; Lack of Activation; Negative Emotional State; Overall Stress. Pressure pain threshold (PPT) was assessed with an algometer (Beslands, Canada) (Pelfort et al., 2015) with the same outcome assessor on three sites (mid points on the rectal femoris, vastus lateralis and gastrocnemius), with the sensor perpendicular to the ROI, data was recorded in triplicate.

2.8. Biomarkers of systemic inflammation, bone turnover and ECM damage

At each time point, after 10-min of seated rest, venous blood samples were collected via venepuncture in EDTA vacutainers for markers of inflammation (e.g., interleukin-6 [IL-6], interleukin-10 [IL-10], Tumor necrosis factor [TNFα]), bone turnover (β-isomerised C-terminal telopeptides [β-CTX], Total Procollagen 1 N-Terminal Propeptide [P1NP]) and ECM damage (hydroxyproline). All venous blood samples were centrifuged at 4,500*g* at 4 °C for 10-min immediately following collection (Heraeus Multifuge 3 S-R, DJB Labcare, Buckinghamshire, UK), with plasma then separated and stored at −80 °C. Plasma IL-6 (DY206; BioTechne, UK), IL-10 (DY217B; BioTechne, UK), TNFα (DY210; BioTechne, UK), β-CTX (orb1807098, Biorbyt, UK), P1NP (abx152747; Abbexa, UK) and hydroxyproline (abx575943; Abbexa, UK) were analysed in duplicate using commercially available ELISA kits and analysed using a plate reader (SpectraMax i3x, Molecular Devices, UK).

2.9. Statistical analysis

Normally distributed data are presented as mean (SD), and non-normally distributed data as median and interquartile range (IQR).

Significant differences were accepted by rejecting the null-hypothesis for $P < 0.05$. Statistical analyses were performed on Statistical Package for the Social Sciences software version 28.0 (SPSS, IBM, Chicago, IL). All data were tested for normality using skewness and kurtosis and, if violated, the square root, was calculated to achieve normal distribution where possible (P1NP, SSS, PPT). For ANOVAs, effect sizes were reported as partial eta squared (η_p^2; small = 0.01; medium = 0.06 and large = 0.14). To test for changes between conditions (i.e., supplements) and time (baseline, 2.5-h, 24-h, 48-h, and 72-h) a 3 × 5-way (condition × time) mixed model ANOVA was utilised. Bonferroni corrected post hoc tests were used to look for where significant differences occurred in the ANOVAs.

3. Results

A total of 40 participants (Table 1) were recruited, 36 of which (12 in each condition) completed all study visits (Fig. 1). Reasons for withdrawal included injury outside of the study visits ($n = 3$), and non-adherence with the intervention, unrelated to the supplements ($n = 1$). The full anonymised dataset has been made freely available as supplementary material on the University of Portsmouth repository (https://doi.org/10.17029/538eb0e3-5d2c-43a8-ba3c-bd605052a46a).

3.1. Jump performance

EIMD reduced CMJ height across time ($F_{(3.754,\ 123.890)} = 6.224$, $p < 0.001$, $\eta_p^2 = 0.159$). Thirty days of Natiiv™ collagen, hydrolysed collagen or placebo supplementation had no effect on CMJ performance ($F_{(2,\ 33)} = 0.400$, $p = 0.673$, $\eta_p^2 = 0.024$) and there was no interaction ($F_{(7.508,\ 123.890)} = 0.709$, $p = 0.674$, $\eta_p^2 = 0.041$; see Fig. 1). EIMD reduced CMJ mRSI ($F_{(3.616,\ 119.337)} = 4.679$, $p = 0.002$, $\eta_p^2 = 0.124$) and DJ mRSI ($F_{(2.147,\ 70.839)} = 5.709$, $p = 0.004$, $\eta_p^2 = 0.147$) performance, but did not effect SJ height ($F_{(3.554,\ 117.273)} = 1.969$, $p = 0.112$, $\eta_p^2 = 0.056$) or EUR ($F_{(3.690,\ 121.771)} = 1.196$, $p = 0.316$, $\eta_p^2 = 0.035$) performance. Supplementation had no effect on CMJ mRSI ($F_{(2,\ 33)} = 0.209$, $p = 0.812$, $\eta_p^2 = 0.013$), SJ height ($F_{(2,\ 33)} = 0.018$, $p = 0.982$, $\eta_p^2 = 0.001$), DJ mRSI ($F_{(2,\ 33)} = 0.140$, $p = 0.870$, $\eta_p^2 = 0.008$) or EUR ($F_{(2,\ 33)} = 3.165$, $p = 0.055$, $\eta_p^2 = 0.161$). No significant interactions were present for; CMJ mRSI ($F_{(7.233,\ 119.337)} = 1.247$, $p = 0.282$, $\eta_p^2 = 0.070$), SJ height ($F_{(7.107,\ 117.273)} = 0.748$, $p = 0.634$, $\eta_p^2 = 0.043$), DJ mRSI ($F_{(4.293,\ 70.839)} = 0.593$, $p = 0.680$, $\eta_p^2 = 0.035$) or EUR ($F_{(7.380,\ 121.771)} = 0.562$, $p = 0.794$, $\eta_p^2 = 0.033$).

3.2. Quadriceps strength

EIMD reduced MVIC across time ($F_{(3.754,\ 123.870)} = 3.223$, $p = 0.017$, $\eta_p^2 = 0.089$). Thirty days of Natiiv™ collagen, hydrolysed collagen, or placebo supplementation had no effect on MVIC performance ($F_{(2,\ 33)} = 0.141$, $p = 0.869$, $\eta_p^2 = 0.008$) and there was no interaction ($F_{(7.507,\ 123.870)} = 1.320$, $p = 0.243$, $\eta_p^2 = 0.047$; see Fig. 2).

Table 1
Participant characteristics.

Parameter	Natiiv™ collagen	Hydrolysed collagen	Placebo	*P*-Value
Age (y)	20.7 (2.3)	20.0 (1.2)	23.1 (6.7)	0.21
Male/Female (*n*)	9/3	9/3	9/3	n/a
Height (m)	1.78 (0.12)	1.76 (0.5)	1.76 (0.10)	0.82
Body mass (kg)	76.2 ± 27.2	73.7 ± 21.1	87.2 ± 30.0	0.59
BMI (kg/m^2)	24.21 ± 3.65	24.17 ± 4.93	27.16 ± 8.43	0.41
MVIC (N)	255 (55)	271 (61)	272 (98)	0.82

Data are presented as means (SD) for parametric data or median ± IQR for non-parametric data ($n = 12$). A one-way ANOVA was used to compare groups with parametric data, a Kruskal-Wallis test was used for non-parametric data. N.B. MVIC, maximal voluntary contraction; BMI, body mass index; y, years; *n*, sample size; m, meters; kg, kilograms; N, newtons; ANOVA, analysis of variance; SD, standard deviation; IQR, inter-quartile range.

3.3. Synovial inflammation

EIMD increased knee joint synovial inflammation across time ($F_{(4,\ 128)} = 2.711$, $p = 0.033$, $\eta_p^2 = 0.078$). Thirty days of Natiiv™ collagen, hydrolysed collagen or placebo supplementation had no effect on synovial inflammation ($F_{(2,\ 32)} = 0.814$, $p = 0.452$, $\eta_p^2 = 0.048$) and there was no interaction ($F_{(8,\ 128)} = 0.732$, $p = 0.663$, $\eta_p^2 = 0.044$; see Fig. 3).

3.4. Leg muscle pain and DOMS

EIMD increased DOMS ($F_{(3.765,\ 124.240)} = 60.905$, $p < 0.001$, $\eta_p^2 = 0.649$), leg muscle pain ($F_{(2.086,\ 68.840)} = 3.684$, $p = 0.029$, $\eta_p^2 = 0.100$), stress ($F_{(2.719,\ 89.712)} = 30.020$, $p < 0.001$, $\eta_p^2 = 0.476$), and reduced recovery capabilities ($F_{(4,\ 132)} = 23.793$, $p < 0.001$, $\eta_p^2 = 0.419$) across time. Thirty days of Natiiv™ collagen, hydrolysed collagen or placebo supplementation had no effect on DOMS ($F_{(2,\ 33)} = 1.032$, $p = 0.367$, $\eta_p^2 = 0.059$), pain ($F_{(2,\ 33)} = 1.169$, $p = 0.323$, $\eta_p^2 = 0.066$), stress ($F_{(2,\ 33)} = 1.007$, $p = 0.376$, $\eta_p^2 = 0.058$), and reduced recovery capabilities ($F_{(2,\ 33)} = 1.387$, $p = 0.264$, $\eta_p^2 = 0.078$) with no interactions for DOMS ($F_{(7.530,\ 124.240)} = 0.489$, $p = 0.853$, $\eta_p^2 = 0.029$), pain ($F_{(4.172,\ 68.840)} = 0.682$, $p = 0.613$, $\eta_p^2 = 0.040$), stress ($F_{(5.437,\ 89.712)} = 1.058$, $p = 0.391$, $\eta_p^2 = 0.060$), and reduced recovery capabilities ($F_{(8,\ 132)} = 0.581$, $p = 0.792$, $\eta_p^2 = 0.034$; see Fig. 4)

3.5. Biochemistry

EIMD had no effect on markers of anti- and inflammatory status (IL-6: $F_{(4.172,\ 68.840)} = 0.682$, $p = 0.613$, $\eta_p^2 = 0.040$; IL-10: $F_{(7.530,\ 124.240)} = 0.489$, $p = 0.853$, $\eta_p^2 = 0.029$; TNFα: $F_{(8,\ 132)} = 0.581$, $p = 0.792$, $\eta_p^2 = 0.034$) across time. Thirty days of Natiiv™ collagen, hydrolysed collagen, or placebo supplementation, had no effect on markers of anti- and inflammatory status (IL-6: $F_{(4.172,\ 68.840)} = 0.682$, $p = 0.613$, $\eta_p^2 = 0.040$; IL-10: $F_{(7.530,\ 124.240)} = 0.489$, $p = 0.853$, $\eta_p^2 = 0.029$; TNFα: $F_{(8,\ 132)} = 0.581$, $p = 0.792$, $\eta_p^2 = 0.034$) with no interactions (IL-6: $F_{(4.172,\ 68.840)} = 0.682$, $p = 0.613$, $\eta_p^2 = 0.040$; IL-10: $F_{(7.530,\ 124.240)} = 0.489$, $p = 0.853$, $\eta_p^2 = 0.029$; TNFα: $F_{(8,\ 132)} = 0.581$, $p = 0.792$, $\eta_p^2 = 0.034$).

EIMD had no effect on markers of bone turnover, or type 1 collagen formation (β-CTX: $F_{(4,\ 116)} = 0.856$, $p = 0.493$, $\eta_p^2 = 0.029$; P1NP: $F_{(4,\ 116)} = 0.357$, $p = 0.839$, $\eta_p^2 = 0.012$; HYP: $F_{(3.143,\ 91.137)} = 0.803$, $p = 0.500$, $\eta_p^2 = 0.027$), across time. Thirty days of Natiiv™ collagen, hydrolysed collagen or placebo supplementation had no effect on markers of bone turnover or type 1 collagen formation (β-CTX: $F_{(2,\ 29)} = 0.658$, $p = 0.525$, $\eta_p^2 = 0.043$; P1NP: $F_{(2,\ 29)} = 0.445$, $p = 0.645$, $\eta_p^2 = 0.030$; HYP: $F_{(2,\ 29)} = 1.971$, $p = 0.157$, $\eta_p^2 = 0.120$) with no interactions (β-CTX: $F_{(8,\ 116)} = 0.767$, $p = 0.633$, $\eta_p^2 = 0.050$; P1NP: $F_{(8,\ 116)} = 0.798$, $p = 0.606$, $\eta_p^2 = 0.052$; HYP $F_{(6.285,\ 91.137)} = 0.946$, $p = 0.469$, $\eta_p^2 = 0.061$; see Fig. 5)

4. Discussion

This is the first study to assess the effects of Natiiv™ collagen in its commercially available dose on 1) jump performance; 2) strength; 3) pain; and biomarkers of 4) inflammation; 5) ECM damage and; 6) bone turnover compared with hydrolysed collagen and placebo following muscle damaging exercise. The principal novel findings were that 30-days of Natiiv™ collagen had no effect on jumping performance, strength, synovial inflammation at the knee joint, leg muscle pain, DOMS, peripheral markers of inflammation and bone turnover, compared to hydrolysed collagen and placebo supplementation in young healthy adults following a 150 drop jump EIMD-inducing protocol.

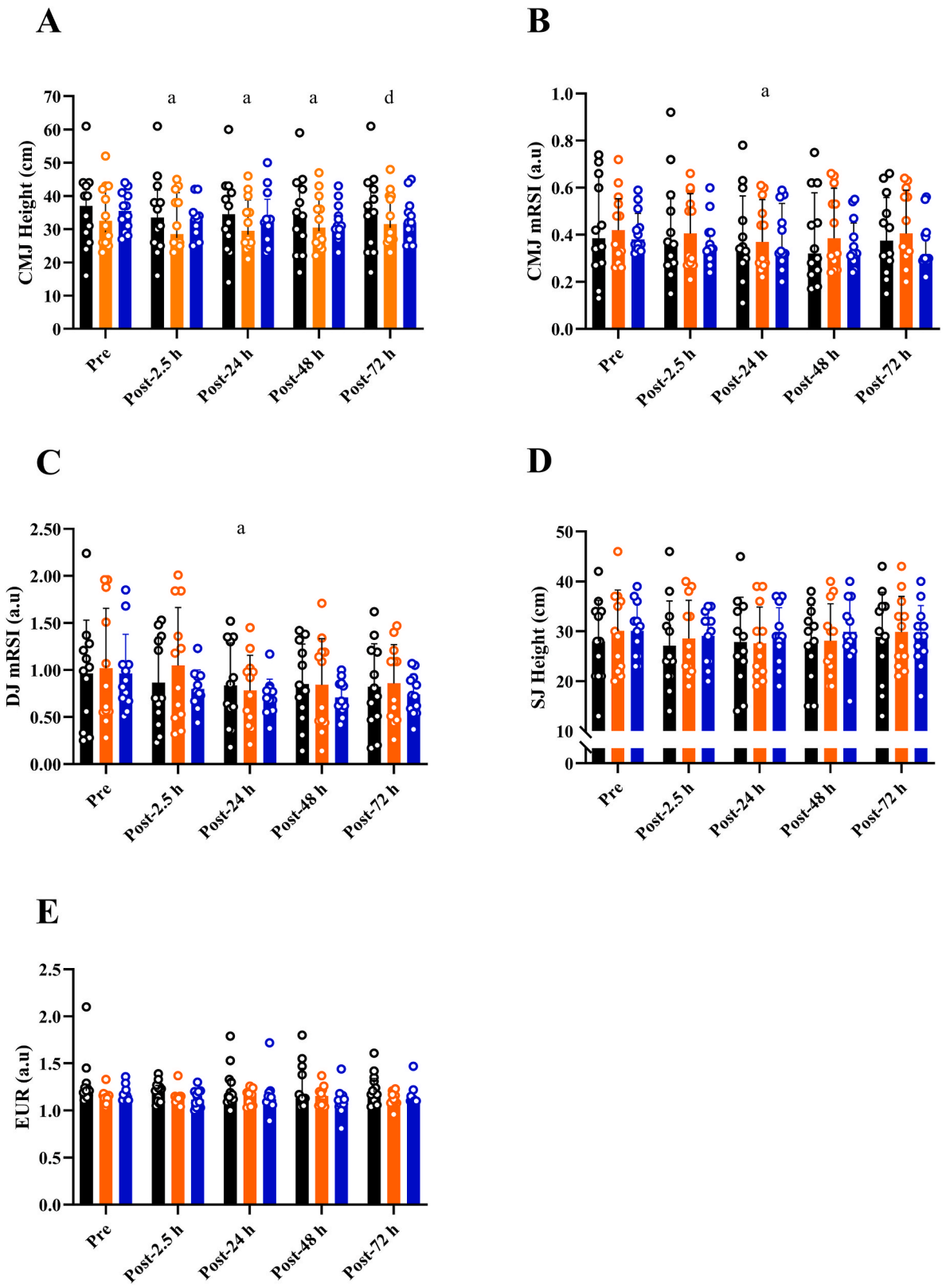

Fig. 1. Effect of ingesting Natiiv™ collagen on (A) countermovement jump (CMJ) height, (B) CMJ modified reactive strength index (mRSI), (C) drop jump (DJ) mRSI, (D) squat jump (SJ) height and (E) eccentric utilisation ratio (EUR) post exercise induced muscle damage (EIMD) compared to hydrolysed collagen and placebo. X-axis represents time relative to EIMD. Data are presented as mean ± SD for C and D and as median ± IQR for A, B and E; $n = 12$ for each group; Natiiv™ = black bar, placebo = orange bar, hydrolysed collagen = blue bar. Letters indicate significant differences ($p < 0.05$) between time points. a = different to Pre, b = different to 2.5 h, c = different to 24 h, d = different to 48 h.

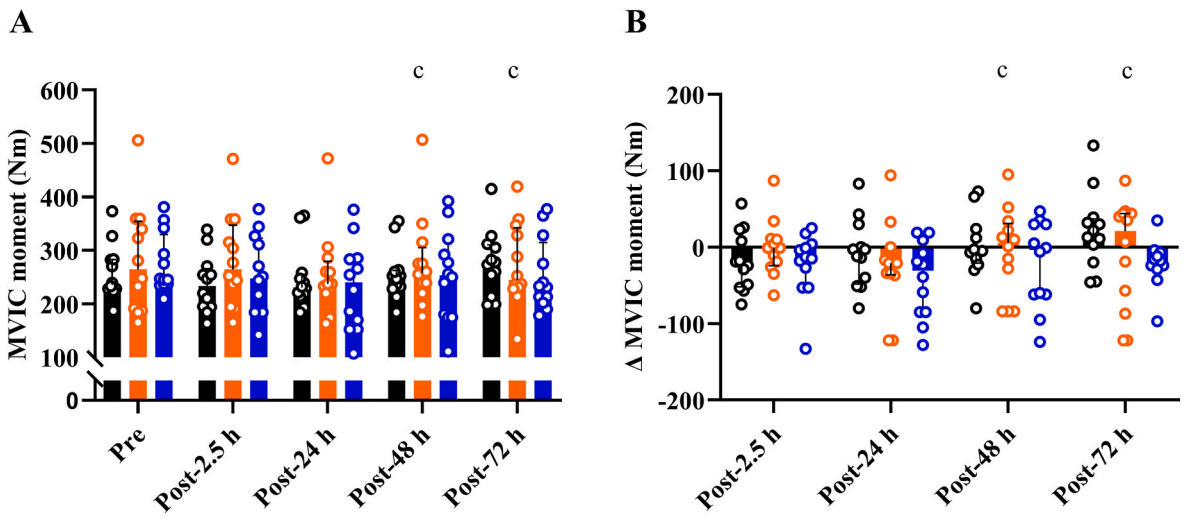

Fig. 2. Effect of ingesting Natiiv™ collagen on maximum voluntary isometric contraction of the quadriceps post exercise induced muscle damage (EIMD) compared to hydrolysed collagen and placebo (A) and corrected for baseline (B). X-axis represents time relative to EIMD. Data are presented as median ± IQR; $n = 12$ for each group; Natiiv™ = black bar, placebo = orange bar, hydrolysed collagen = blue bar. Letters indicate significant differences ($p < 0.05$) between time points. a = different to Pre, b = different to 2.5 h, c = different to 24 h, d = different to 48 h.

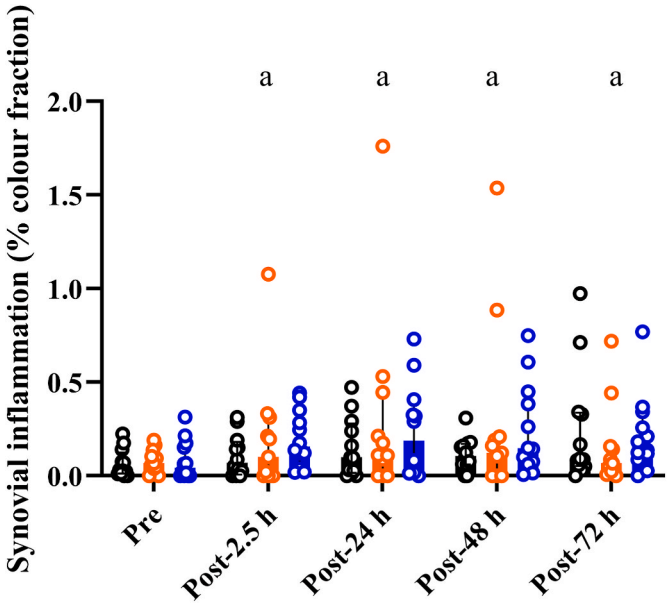

Fig. 3. Effect of ingesting Natiiv™ collagen on colour fraction sonography of the knee post exercise induced muscle damage (EIMD) compared to hydrolysed collagen and placebo. X-axis represents time relative to EIMD. Data are presented as median ± IQR; $n = 12$ for Natiiv™, $n = 11$ for placebo and $n = 12$ for hydrolysed collagen; Natiiv™ = black bar, placebo = orange bar, hydrolysed collagen = blue bar. Letters indicate significant differences ($p < 0.05$) between time points. a = different to Pre, b = different to 2.5 h, c = different to 24 h, d = different to 48 h.

4.1. Jump performance and strength

Natiiv™ is rich in fibrillar type I collagen and can theoretically increase delivery of its constituent amino acids and intact alpha helices to the ECM to support more rapid repair following intensive exercise. For the first time, we have shown that 30-days of Natiiv™ collagen supplementation had no effect on jump performance following recovery from muscle damaging exercise compared to hydrolysed collagen or placebo. This was in contrast to previous published work that has shown supplementation of hydrolysed collagen for only 7-days to improve recovery in jumping performance (specifically CMJs) in recreationally active individuals. Whilst these equivocal findings are difficult to explain given the comparable doses of hydrolysed collagen (20 g·day^{-1}) (Clifford et al., 2019) ingested, and similar EIMD-inducing protocols. However, in the present study we assessed BUCS athletes which may have differences in diet, history in plyometrics exercises which may explain the differences in results between these groups. One possible explanation could be that there is a difference in how jump height is calculated between these studies (i.e. flight time vs impulse-momentum relationship) which may at least in part explain the difference seen. The present study supplementation period was, however, longer (7- vs. 30-days). One potential reason for the differences in findings could be due to a longer time between initiation of supplementation and follow-up visits, which could increase the effects of confounding variables, including lifestyle factors, to remodelling of collagen-rich tissues. Similarly, we also demonstrated that 30-days of Natiiv™ collagen supplementation had no effect on MVIC recovery compared to hydrolysed collagen or placebo. During production, hydrolysed collagen is broken down into smaller peptide chains. Natiiv™ collagen potentially increases delivery of its constituent amino acids and intact alpha helices to the extracellular matrix (ECM) for remodelling aiding in recovery and, therefore, strength. Despite this, we did not observe a statistically significant improvement in recovery of strength. One possible explanation could be that the alpha helices are being denatured in the stomach (REUTERSWÄRD & FABIANSSON, 1985) or that the dose (0.255 g of Natiiv™ collagen) was too low. A limitation of our study was the lack of assessment of bioavailability. Future studies should, therefore, first assess the bioavailability of alpha helices following Natiiv™ collagen consumption and, if necessary, explore interventions that may increase the bioavailability of Natiiv™ collagen by protecting it from the acidic environment of the stomach. Although we utilised an *a-priori* power calculation, one other potential explanation could simply be that we were underpowered to detect a difference in MVIC. This is supported by MVIC data 72-h after EIMD, where MVIC following Natiiv™ collagen supplementation appears to be ~23 % higher than hydrolysed collagen, with a medium effect size ($\eta^2 = 0.047$). Whilst an interesting finding, caution should be taken when interpreting this finding until future studies can corroborate this secondary analysis.

This study was the first to explore the effect of collagen supplementation following EIMD on jumping tasks with low (i.e., SJ) and high (i.e., DJ) stretch shortening cycle demands. Muscle tendon unit mechanics have been shown to differ between these jump types with

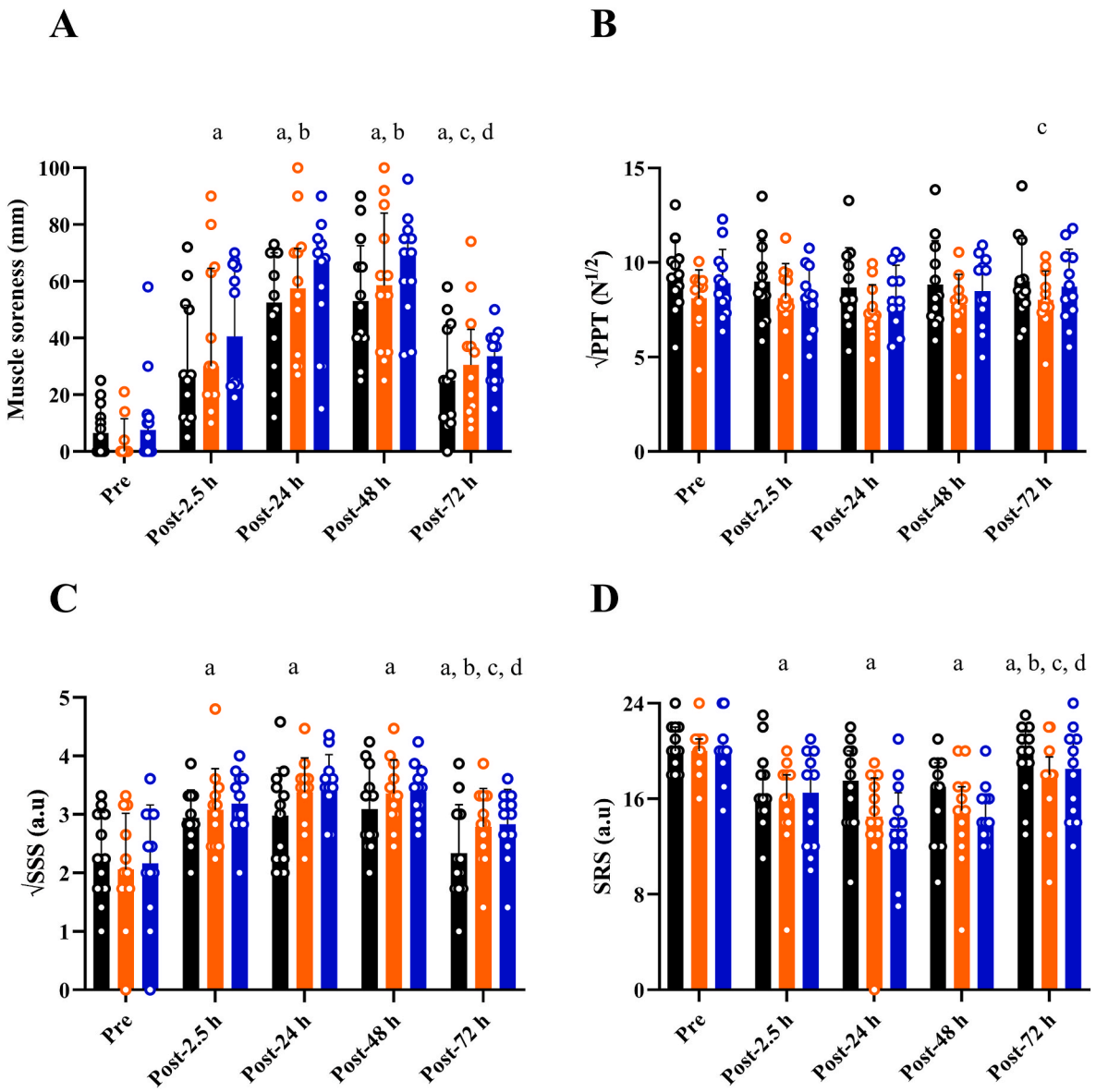

Fig. 4. Effect of ingesting Natiiv™ collagen on (A) muscle soreness visual analogue scale, (B) square root pressure pain threshold (PPT) of the leg, (C) square root short stress score (SSS) and (D) short recovery score (SRS) post exercise induced muscle damage (EIMD) compared to hydrolysed collagen and placebo. X-axis represents time relative to EIMD. Data are presented as mean ± SD for B and C and as median ± IQR for A and D; $n = 12$ for each group; Natiiv™ = black bar, placebo = orange bar, hydrolysed collagen = blue bar. Letters indicate significant differences ($p < 0.05$) between time points. a = different to Pre, b = different to 2.5 h, c = different to 24 h, d = different to 48 h.

greater fascicle lengthening in lower SSC movements, and larger changes in tendon length in high SSC movements (Kurokawa et al., 2001, 2003). The absence of any differences identified in the effect of collagen supplementation across the jumps tested, support the conclusion that collagen did not have any effect on the recovery of contractile or non-contractile components of the muscle tendon unit following EIMD. Given the greater role collagen plays in the makeup of non-contractile components it is possible that its capacity to facilitate tissue recovery may be differential to different components of the muscle tendon unit and warrants further exploration.

4.2. *Systemic and synovial inflammation and leg muscle pain*

We reported an increase in synovial inflammation post muscle damaging exercise, however, this was unaffected by 30-days of Natiiv™ collagen supplementation, or hydrolysed collagen compared to placebo. This is in line with Clifford et al. (2019), who showed no effect of collagen supplementation on systemic markers of inflammation following EIMD. It is, though, worthy of note that animal (e.g., rat (Dar et al., 2017) and mouse (Mizumura & Taguchi, 2016)) models suggest that collagen supplementation could improve EIMD related inflammation, however caution should always be applied since findings from animal studies do not always readily translate to humans. Moreover, Natiiv™ collagen supplementation had no effect on leg muscle pain or muscle soreness recovery following EIMD, compared to hydrolysed collagen or placebo, in the present study – in line with prior research (Clifford et al., 2019; Lopez et al., 2015). The reason for a lack of effect in healthy adults may simply be that the extent of the pain/muscle soreness is subclinical and a larger effect of muscle damaging exercise is needed to detect notable effects on pain and muscle soreness, especially given its clear positive effects in clinical populations (Kumar et al., 2015; Woo et al., 2017; Zdzieblik et al., 2017).

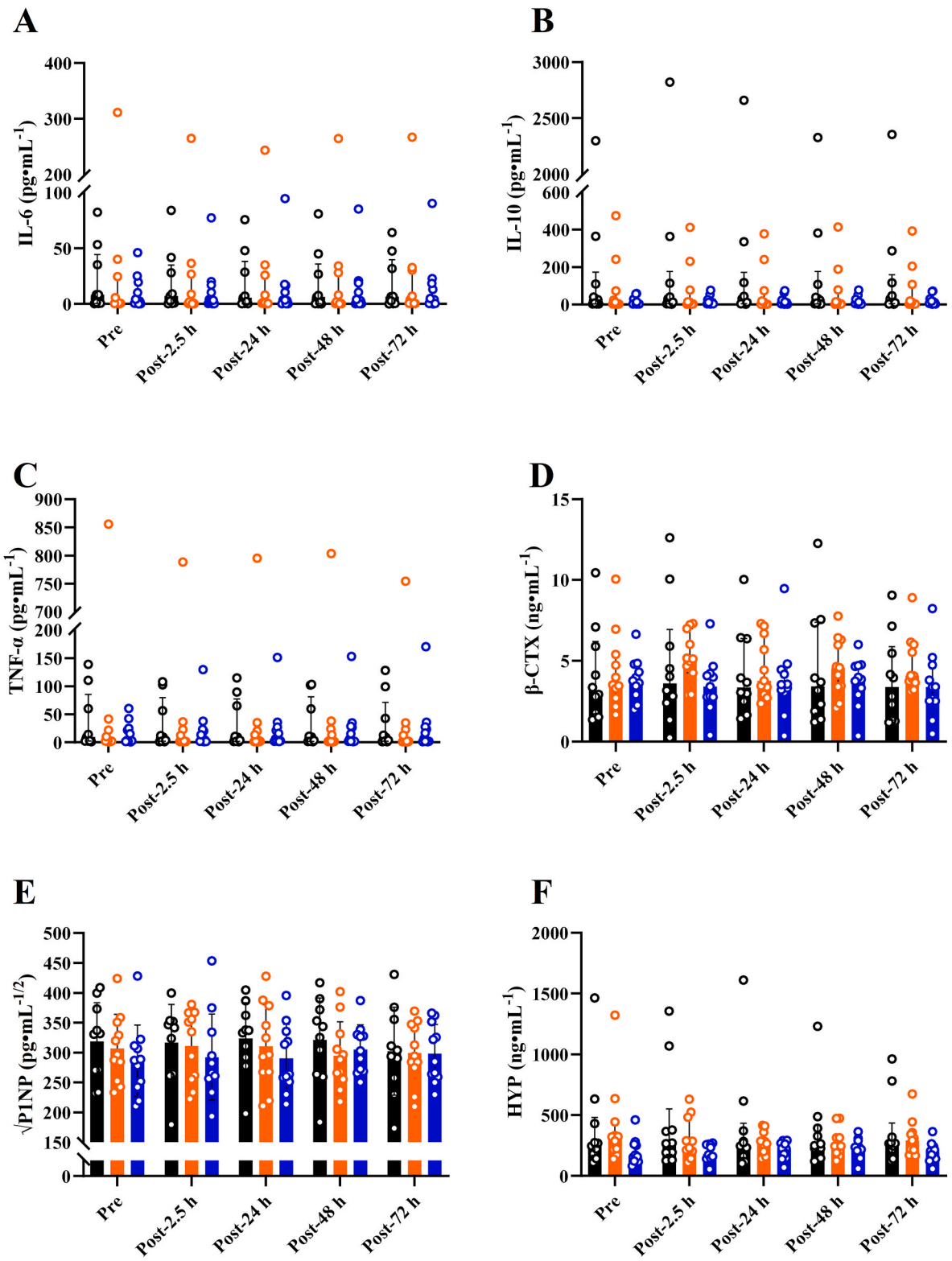

Fig. 5. Effect of ingesting Natiiv™ collagen on plasma (A) interleukin-6, (B) interleukin-10, (C) tumour necrosis factor alpha, (D) beta C–terminal telopeptide, (E) square root procollagen 1 N-terminal propeptide and (F) hydroxyproline, post exercise induced muscle damage (EIMD) compared to hydrolysed collagen and placebo. X-axis represents time relative to EIMD. Data are presented as mean ± SD for E and as median ± IQR for A, B, C, D and F; for panel A $n = 9$ for Natiiv™, $n = 11$ for placebo and $n = 11$ for hydrolysed collagen; for panel B $n = 10$ for Natiiv™, $n = 11$ for placebo and $n = 11$ for hydrolysed collage; for panel C $n = 9$ for Natiiv™, $n = 11$ for placebo and $n = 11$ for hydrolysed collagen; for panel D $n = 10$ for Natiiv™, $n = 11$ for placebo and $n = 11$ for hydrolysed collagen; for panel E $n = 10$ for Natiiv™, $n = 11$ for placebo and $n = 11$ for hydrolysed collagen; for panel F $n = 10$ for Natiiv™, $n = 11$ for placebo and $n = 11$ for hydrolysed collagen; Natiiv™ = black bar, placebo = orange bar, hydrolysed collagen = blue bar.

4.3. Bone turnover

Dietary collagen has the potential to enhance bone turnover, particularly by providing ample glycine and proline as precursors for de novo collagen synthesis (Eastoe, 1955; Alcock et al., 2019). However, in the present study, 30-days of Natiiv™ collagen supplementation had no effect on bone turnover (P1NP, β-CTX) or type 1 collagen formation (hydroxyproline) following muscle damaging exercise, compared to hydrolysed collagen or placebo supplementation. However, it is pertinent to note that previous studies on collagen supplementation (both gelatin and hydrolysed collagen) have shown conflicting results on and β-CTX and P1NP with some studies showing increased concentrations (König et al., 2018; Shaw et al., 2017) and others showing no effect (Clifford et al., 2019). The differences in observations for bone turnover biomarkers are unclear and warrant further investigation. However, the duration of supplementation does not appear to be fundamental given the range of timings in published work 1-h (Shaw et al., 2017): 7-days (Clifford et al., 2019): 12-months (König et al., 2018): and ourselves at 30 days.

4.4. Experimental considerations

The research design used herein (a balanced, double-blind, randomised control trial) is a key strength, of this study to investigate the effects of Natiiv™ collagen in its commercially available dose on exercise performance; strength; pain; and biomarkers of inflammation; ECM damage and; bone turnover following muscle damaging exercise. The primary limitation of this work is the indirect nature of assessing inflammation, muscle strength, and ECM damage. Whilst peripheral biomarkers of inflammation give some insight into local muscle damage and inflammation (Arnold et al., 2017), they do not represent direct assessments. While previous work utilising the same EIMD protocol has elicited EIMD (Clifford et al., 2019), we show that numerous EIMD outcome measures show that they may not have responded to the EIMD protocol. This may at least in part be due to our cohort having been well-trained. Logistical reasons meant we did not collect muscle biopsies but future trials in the area should consider taking skeletal muscle samples, albeit there may be some localised inflammation which would need to be accounted for. Likewise, colour fraction ultrasonography gives a great insight into local synovial joint inflammation, but it is not a direct measure. Caution should be taken when interpreting these results given these are secondary outcome measures that we were not powered to detect changes in. We were also unable to assess post-prandial bioavailability in this study. Future studies should assess the availability of amino acids and, specifically, alpha helices, following Natiiv™ collagen ingestion. The dosing between the hydrolysed collagen (20 $g \cdot day^{-1}$) and the Natiiv™ collagen (0.255 $g \cdot day^{-1}$) were sufficiently different and reflects what is commercially available and we acknowledge the different protein doses within this pragmatic RCT. Future studies should assess whether higher doses for Natiiv™ collagen would yield different results. We also acknowledge the limited extent of muscle damage observed (e.g., ~10 % reduction in 24-h force), compared with other studies, likely owing to the population assessed (i.e., highly physically active, and likely accustomed to eccentric-type exercise) and may, in-part explain the lack of difference between the recovery of the groups. Nevertheless, given the primary rationale for the efficacy of collagen supplementation post-muscle damage, we feel that this was the most ecologically valid and appropriate population to study. Furthermore, maximal effort produced on the jumps was always subjective and not confirmed with an objective measure such as electrical stimulation. Maximal effort was determined by the researcher by checking to make sure that all triplicate jumps were close together and not all improving. Finally, in this study we limited diet assessment to 24 h recall only and did not strictly control dietary intake. This was done to increase ecological validity of the study. Whilst our decision not to strictly control diet maximises the ecological validity of our findings, we were unable to precisely determine habitual intake of protein and collagen-rich sources that may have confounded our results. The current study only investigated recovery up to 72 h post-EIMD. Potentially, there could be longer-term benefits of collagen supplementation on muscle recovery and future research should also aim to investigate over longer periods (e.g. 12 weeks).

5. Conclusion

This is the first study to assess the effects of Natiiv™ collagen in its commercially available dose on 1) jump performance; 2) strength; 3) pain; and biomarkers of 4) inflammation; 5) ECM damage and; 6) bone turnover compared with hydrolysed collagen and placebo following EIMD. In contrast to our hypotheses, we found that 30 days of Natiiv™ collagen had no effect on recovery of jump performance, strength, pain; or biomarkers of inflammation, ECM degradation or bone turnover compared to hydrolysed collagen or placebo supplementation.

CRediT authorship contribution statement

Thomas J. James: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Harry Mayes:** Writing – review & editing, Investigation, Data curation. **Mohammad Alnajjar:** Writing – review & editing, Investigation, Data curation. **Yasmin Newell:** Writing – review & editing, Investigation, Data curation. **Eliska Kohlert:** Writing – review & editing, Investigation, Data curation. **Janis Shute:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Data curation. **Maria Perissiou:** Writing – review & editing, Funding acquisition, Conceptualization. **Jo Corbett:** Writing – review & editing, Conceptualization. **Joseph T. Costello:** Writing – review & editing, Funding acquisition, Conceptualization. **Emma Neupert:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Joseph M. Moore:** Writing – review & editing, Project administration, Funding acquisition, Data curation, Conceptualization. **Paul T. Morgan:** Writing – review & editing, Funding acquisition, Conceptualization. **Chris Simms:** Writing – review & editing, Funding acquisition, Conceptualization. **Zoe L. Saynor:** Writing – review & editing, Funding acquisition, Conceptualization. **Anthony I. Shepherd:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Funding and conflicts of interest

This work was funded by the Trinsic collagen limited. Trinsic collagen has input into the design of the study (number of outcome visits) and produced the Natiiv™ product, but had no input into the investigation, data collection, analysis, interpretation or dissemination of the findings.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Anthony I. Shepherd reports equipment, drugs, or supplies was provided by Trinsic Collagen Limited. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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