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Whey protein hydrolysate augments tendon and muscle hypertrophy independent of resistance exercise contraction mode

J. Farup[1], S. K. Rahbek[1], M. H. Vendelbo[2], A. Matzon[1], J. Hindhede[1], A. Bejder[1], S. Ringgard[3], K. Vissing[1]

[1]Section of Sport Science, Department of Public Health, Aarhus University, Aarhus, Denmark, [2]Department of Internal Medicine and Endocrinology, Aarhus University Hospital, Aarhus,Denmark, [3]MR-Research Centre, Institute of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark

Corresponding author: Jean Farup, Section of Sport Science, Department of Public Health, Aarhus University, Dalgas Avenue 4, DK-8000 Aarhus, Denmark. Tel: +45 8716 8178, Fax: +45 87150201, E-mail: jean@sport.au.dk

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In a comparative study, we investigated the effects of maximal eccentric or concentric resistance training combined with whey protein or placebo on muscle and tendon hypertrophy. 22 subjects were allocated into either a high-leucine whey protein hydrolysate + carbohydrate group (WHD) or a carbohydrate group (PLA). Subjects completed 12 weeks maximal knee extensor training with one leg using eccentric contractions and the other using concentric contractions. Before and after training cross-sectional area (CSA) of m. quadriceps and patellar tendon CSA was quantified with magnetic resonance imaging and a isometric strength test was used to assess maximal voluntary contraction (MVC) and rate of force development (RFD). Quadriceps CSA increased by 7.3 ± 1.0% ($P < 0.001$) in WHD and 3.4 ± 0.8% ($P < 0.01$) in PLA, with a greater increase in WHD compared to PLA ($P < 0.01$). Proximal patellar tendon CSA increased by 14.9 ± 3.1% ($P < 0.001$) and 8.1 ± 3.2% ($P = 0.054$) for WHD and PLA, respectively, with a greater increase in WHD compared to PLA ($P < 0.05$), with no effect of contraction mode. MVC and RFD increased by 15.6 ± 3.5% ($P < 0.001$) and 12–63% ($P < 0.05$), respectively, with no group or contraction mode effects. In conclusion, high-leucine whey protein hydrolysate augments muscle and tendon hypertrophy following 12 weeks of resistance training – irrespective of contraction mode.

Single-bout resistance exercise in the fed state is commonly associated with an increased net protein synthesis, which, when repeated during extended periods of resistance training, will expectedly accumulate into hypertrophy of skeletal muscle tissue and presumably also influence growth in interconnected tissues like tendon and bone (Folland & Williams, 2007; Kongsgaard et al., 2007; Atherton & Smith, 2012). Resistance exercise inherently involving both eccentric and concentric muscle contractions ("conventional resistance exercise", CRE), has previously been demonstrated to provoke not only muscle, but also tendon hypertrophy (Folland & Williams, 2007; Hartman et al., 2007; Kongsgaard et al., 2007; Hulmi et al., 2009; Farup et al., 2012).

The degree of resistance exercise-induced muscle protein synthesis is highly influenced by dietary protein supplementation (Atherton & Smith, 2012). Accordingly, protein supplementation enriched with branched chain amino acids (e.g. leucine) provided immediately following resistance exercise, augment post-exercise muscle protein synthesis (MPS; Wolfe, 2006; Wilkinson et al., 2007; Hulmi et al., 2010). On the other hand, investigations on additive effects of prolonged (i.e. > 10 weeks) CRE training combined protein supplementation are less conclusive. Accordingly, some studies report augmented muscle hypertrophy following CRE training combined with timed protein ingestion in comparison to non-energetic (Esmarck et al., 2001) or isoenergetic placebo (Andersen et al., 2005; Hartman et al., 2007), whereas others report identical changes from CRE with whey compared to placebo supplementation (Verdijk et al., 2009; Erskine et al., 2012).

Alternatively, muscle contraction mode may comprise another means to influence the degree of muscle hypertrophy. In this regard, the ability to develop higher forces during eccentric compared to concentric contractions is recognized; consequently, the concentric strength will stipulate the absolute loading conditions during CRE (Crenshaw et al., 1995). However, higher contraction forces combined with a lower energy cost (Beltman et al., 2004) and/or altered fiber recruitment pattern (Nardone et al., 1989), renders it plausible that eccentric contractions may entail superior potential to provoke hypertrophy changes compared to concentric contraction mode, and this is supported by findings that eccentric exercise promote superior initial MPS (Moore et al., 2005). Still, it is not firmly established, whether this also accumulates into augmented hypertrophy with prolonged eccentric training (Roig et al., 2009) with

some studies having observed greater hypertrophy following eccentric compared to concentric training (Higbie et al., 1996; Vikne et al., 2006) while other studies have failed to observe any difference in hypertrophy (Blazevich et al., 2007; Moore et al., 2012).

In addition to skeletal muscle hypertrophy, interconnected tendon tissue has also been shown to respond to resistance exercise training. Accordingly, some, but not all studies have observed increases in patellar tendon cross-sectional area (CSA) following heavy-load CRE training (Kongsgaard et al., 2007; Seynnes et al., 2009). The influences of loading intensity and/or contraction mode on tendon growth have not been directly investigated. However, cross-sectional data from elite badminton players and fencers indicates a greater patellar tendon CSA in the lead leg (i.e. exposed to high eccentric loads; Couppe et al., 2008) and a longitudinal study comparing the patellar tendon adaptations to heavy vs light load conventional resistance training indicates a greater hypertrophy adaptation in the heavy leg (Kongsgaard et al., 2007). Collectively, these findings suggest that loading intensity and/or contraction mode comprise driving factors for tendon hypertrophy. Moreover, the effect of protein supplementation combined with resistance training on tendon hypertrophy has not previously been investigated, although a recent study indicates a potentially important role for the amino acid leucine in collagen synthesis in rodents (Barbosa et al., 2012).

In a comparative approach, we investigated whether whey protein combined with prolonged eccentric resistance training exhibit superior capability in promoting skeletal muscle and tendon hypertrophy compared to concentric and placebo intervention. The aim of the study was therefore to investigate the effect of 12 weeks of either maximal eccentric or concentric resistance training combined with either a high-leucine whey protein hydrolysate + carbohydrate supplement or isoenergetic carbohydrate placebo, on quadriceps muscle and patellar tendon hypertrophy.

We hypothesized that whey protein hydrolysate high in leucine would augment muscle and tendon hypertrophy. Furthermore, we hypothesized that the isolated eccentric exercise training would augment muscle and tendon hypertrophy compared to isolated concentric exercise training.

Materials and methods

Participants

Twenty-two healthy young recreationally active men were included in the study (mean ± SEM; height 181.5 ± 1.5 cm, weight 78.1 ± 1.8 kg, age 23.9 ± 0.8 years, fat% 16.0 ± 0.9%). All subjects were informed of the purpose and risks of the study and provided written informed content in accordance with the Declaration of Helsinki and approved by local ethical committee of Region Midtjylland (j. no. M-20110003). Exclusion criteria were (a) participation in systematic resistance or high-intensity training for lower extremity muscles within 6 months prior to participation, (b) a history of musculoskeletal lower extremity injuries, (c) vegans, and (d) use of dietary supplements or prescription medication that potentially could influence muscle size or function.

Study design

This long-term training study design was conducted in a double-blinded fashion in relation to dietary supplementation. Following inclusion, subjects were equally allocated into either a high-leucine whey protein hydrolysate + carbohydrate group (WHD, $n = 11$) or an isoenergetic placebo group (PLA, $n = 11$). Regardless of supplementary intake, all subjects performed eccentric training with one leg and concentric training with the other. This within-subject design was used to minimize the potential differences in the hypertrophy response that are inherent with group designs (e.g. initial training status, habitual nutritional intake, and/or hormonal status). Eccentric leg was randomly chosen to be either the dominant (preferred kicking leg) or the nondominant leg to exclude any potential pre-training difference between the two. Accordingly, the following four interventions were compared: eccentric + WHD, eccentric + PLA, concentric + WHD and concentric + PLA. Throughout the study period, the subjects were instructed to maintain their normal habitual physical activity level and dietary intake. Subjects were instructed not to engage in high-intensity activities 48 h before pre- and post-training tests/measurements, not to consume alcohol, and to maintain normal habitual dietary intake (especially to minimize fluid shift). In the 2 weeks before commencing the training program, magnetic resonance imaging (MRI) scans of both thighs and patellar tendons and isometric strength test was performed. All tests were performed at the same time of the day, pre- and post-training, to control for potential effects of diurnal rhythm. The isometric strength test was preferably performed after the MRI scan.

Resistance training

The subjects completed 33 training sessions during the 12 weeks of training. The training program was primarily designed to induce hypertrophy and to a lesser extent maximal muscle strength highlighted by a large number of sets and repetitions and by moderate-high intensity (see below). This duration and type of training program has previously been shown to induce muscle hypertrophy using conventional resistance exercise (Holm et al., 2008).

Training frequency was three times per week with a progressive increase in volume and intensity throughout the 12 weeks. All resistance training sessions were commenced with a standardized warm-up consisting of a 5-min light aerobic exercise (~100 W) on a stationary ergometer cycle (Monark, Varberg, Sweden). The resistance training exercise consisted of isolated knee extensions in a Technogym knee extensor machine (Technogym-Selection line, Technogym, Cesena, Italy). All repetitions were performed by lifting the load with the concentric leg (while extending the eccentric leg unloaded). Then, with aid from a training supervisor, an additional load was released onto the weight stack and then lowered with the eccentric leg. The load for the eccentric leg was aimed at 120% of concentric loading corresponding to the approximate strength difference between slow eccentric and concentric contractions during isokinetic strength testing (Aagaard et al., 2000). Both the eccentric and concentric leg training program consisted of isotonic knee extensions [repetition loading equal to repetition maximum (RM)] with the following set × repetitions; 6 × 10-15RM (sessions 1–4), 8 × 10-15RM (sessions 5–10), 10 × 10-15RM (sessions 11–20), 12 × 6–10 RM (sessions 21–28), and 8 × 6-10RM (sessions 29–33). Subjects were instructed to perform each repetition in a controlled manner (2 s tempo) during both the concentric and the eccentric part of the exercise with two minutes of recovery interspaced between sets.

Table 1. Essential amino acid and peptide profile of the hydrolyzed whey protein product. Percent distribution is calculated relative to total amino acid content

Amino acid profile		
	Total grams per drink (g)	Percent distribution (%)
Histidine	0.41	2.1
Isoleucine	1.29	6.6
Leucine	2.77	14.2
Lysine	1.50	7.7
Methionine	0.35	1.8
Phenylalanine	0.90	4.6
Threonine	1.46	7.5
Tryptophan	0.37	1.9
Valine	1.35	6.9
ΣEAA	9.98	53.3
ΣBCAA	5.40	27.7
Peptide profile		
Molecular weight (daltons)	Number of residues	Percent distribution (%)
< 375	1–3	75.7
375–750	4–6	19.6
> 750	> 7	4.7

All training was closely supervised and monitored by qualified training instructors to ensure proper execution and loading. The total volume load for each leg was calculated (load × repetitions × sets), which is representative of the total work done since range of motion was the same for both legs.

Supplementation

On all training days, the subjects received a drink containing either high-leucine whey protein hydrolysate + carbohydrate (glucose) or isoenergetic carbohydrate (glucose) alone. The subjects ingested half before and half after training. Each drink consisted of an 8% solution (663 KJ) with the whey drink consisting of 19.5 g whey protein hydrolysate (produced by Arla Foods Ingredients Group P/S, Viby J., Denmark) + 19.5 g of carbohydrate (both equal to 4% solution) and the placebo drink consisting of 39 g of carbohydrate. The whey protein hydrolysate was produced by standard filtration techniques to increase the content of leucine and other branched chain amino acids (BCAA; Table 1) above the level of standard milk-based whey protein sources (Hulmi et al., 2010). The subjects were only allowed water *ad libitum* 1 1/2 h prior to and the immediate 1 h after completion of an exercise session, to ensure and standardize the conditions for digestion/absorption and within the range typically applied (Andersen et al., 2005; Hartman et al., 2007; Hulmi et al., 2009). Subjects were instructed to maintain their normal habitual dietary intake throughout the study; however, they did not register their dietary intake since most previous studies using young male subjects observe no difference in habitual total energy or protein intake (Andersen et al., 2005; Hartman et al., 2007; Hulmi et al., 2009; Erskine et al., 2012).

Muscle and tendon CSA

Subjects were seated in a resting position for 30–45 min before entering the scanner and instructed not to move when lying in the scanner. A minimum of 48–72 h was interspaced between the last training session and MRI scanning to minimize the risk of fluids shift. All imaging for both muscle and tendon were performed with a 1.5-T scanner (Philips Achieva, Best, the Netherlands). The subjects were placed in supine position with the feet entering the scanner first, the legs fully extended and a distance between the feet of approximately 10 cm. The MRI scans were performed on both legs using either the body coil (for muscle CSA) or a cardiac coil (for patellar tendon). The later offline analysis (for both muscle and patellar tendon) was conducted using a free software program (Osirix, 4.1.1, Osirix Foundation, Geneva, Switzerland). All scanning parameters for both muscle and tendon examinations were in accordance with previous studies (Kongsgaard et al., 2007; Farup et al., 2012).

Thigh muscle

After an initial frontal survey scan, 50 transversal slices were acquired, of which only three were used for the present study. The first slice was 70 mm proximal to the distal part of the femur condyles and the other slices were acquired proximally from this point. A T1-weighted, fast spin echo sequence with the following parameters was used: scan matrix = 576 × 576, field of view = 46 × 46 cm, number of slices = 50, slice thickness = 7 mm, slice gap = 3 mm, repetition time = 2 s, echo train length = 18, number of signal averages = 2, TR = 500 ms, TE = 6.2 ms, and pixel size = 0.8 × 0.8 mm. From the frontal and transverse scans, the femur length (from the femur condyles to the apex of the trochanter) was calculated. Following this, the knee extensor muscle CSA (mm. vastus lateralis, vastus medialis, vastus intermedius, and rectus femoris) was manually outlined at 1/3, 1/2, and 2/3 of the femur length representing a distal, mid, and proximal level, respectively. For the further analysis only the mid-level CSA and the sum (ΣCSA = distal + mid + proximal) was used. All analyses were conducted by an investigator blinded with regards to intervention (supplementation and contraction type). The CSA calculations were performed three times [mean intraclass correlation (ICC) = 0.99] and the mean value was used for further analysis.

Patellar tendon

An initial sagittal scan was performed on both legs to enable localization of the patellar tendon and for use in the later regional CSA analysis. Following this, an axial scan of the patellar tendon was performed starting from the apex of the patellar. Both scans were T1-weighted, fast spin echo sequences with the following parameters: scan matrix = 500 × 500, field of view = 40 × 40 cm, number of slices = 20, slice thickness = 5 mm, slice gap = 0 mm, repetition time = 2 s, echo train length = 18, number of signal averages = 2, TR = 400 ms, TE = 6.7 ms, and pixel size = 0.8 × 0.8 mm. From the length of the patellar tendon, using the sagittal scans, three regions were defined: (a) proximal (just distal to the insertion on the patellar), (b) distal (just proximal to the insertion on tibia, and (c) midway between the two (Fig. 1). Previous studies have shown this division to be important (Kongsgaard et al., 2007; Seynnes et al., 2009). The patellar tendon CSA was manually outlined using the Osirix software program. The mean of three measures (mean ICC = 0.97) was used for further analysis. All image analysis was conducted by a blinded (with regards to intervention supplementation and contraction type) investigator. To examine if CSA differed along the length of the patellar tendon, we used pre values for all groups since there was no significant differences at this time.

Isometric strength performance

Subsequent to a standardized warm-up consisting of a 5-min low-intensity exercise on a stationary ergometer cycle (Monark), the

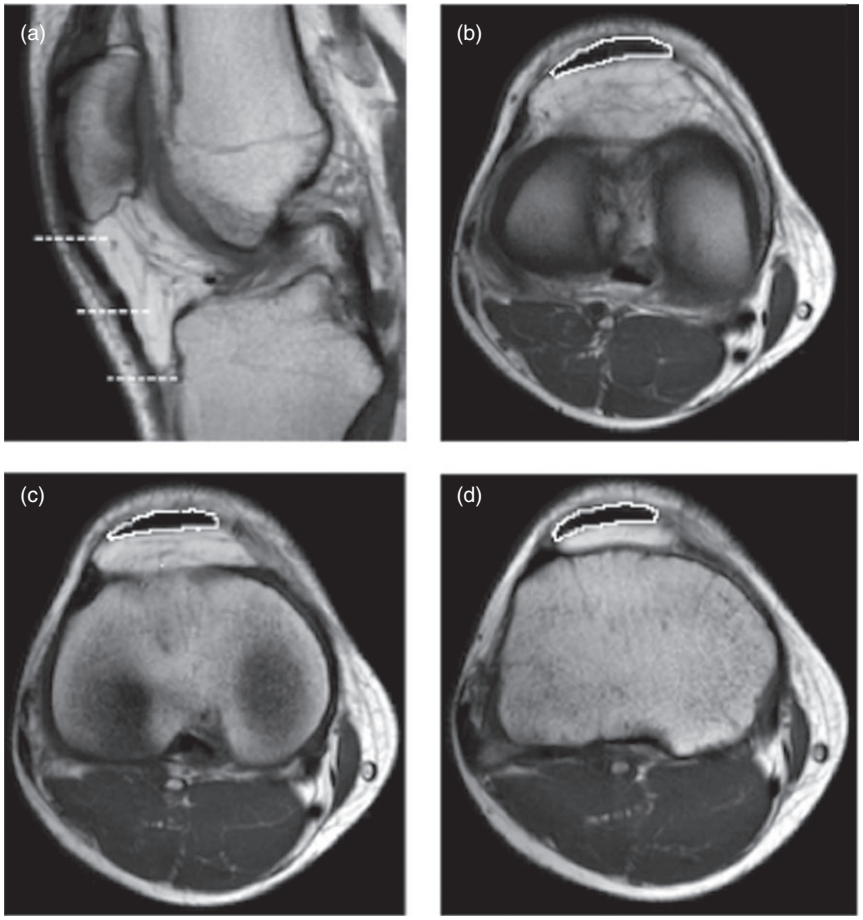

Fig. 1. Saggital and axial depiction of the patellar tendon. Slides were obtained just proximal to the tibial insertion, at mid-level and just distal to the patellar as indicated by the dashed lines (a). The CSA of the patellar tendon was manually outlined at the proximal (b), mid (c), and distal (d) tendon level.

subjects were seated in an isokinetic dynamometer (Humac Norm, CSMI, Stoughton, Massachusetts, USA) with 90° hip flexion and restraining straps crossing the torso and tested leg. Both legs were tested since they were trained differently and the test order was randomized between the eccentric and concentric leg. The transverse axis of the subject's knee was aligned with the axis of the dynamometer. The test leg was attached to the dynamometer arm while the other leg was placed behind a stabilization bar. The dynamometer was adjusted individually so the contact point between the subjects' leg and the dynamometer arm was 3 cm proximal to the malleolus medialis. MVC was measured at 70° knee flexion (0° equals full extension). Before starting the test, the subject's lower leg was weighed to enable gravity correction of the measured torque. The subject was allowed four trials (however, if a subject continued to improve additional trials were provided) and all contractions were interspaced with 1 min recovery time. All trials were sampled at 1500 Hz. The offline analyses were performed in custom-made software (Labview 2011, National Instruments Corporation, Austin, Texas, USA). Maximal voluntary contraction was determined as the highest peak torque from the best of the four trials and this trial was used for further analysis. Rate of force development (RFD; Nm/s) was defined as the slope of the torque-time curve in incrementing time periods of 0–30, 0–50, 0–100, and 0–200 ms and normalized RFD was defined as the slope at 1/6, 1/2, and 2/3 of MVC from the onset of contraction (Blazevich et al., 2008). Contractile impulse (Nm*s) was calculated as the torque-time integral in time steps of 0–30, 0–50, 0–100, and 0–200 ms from the onset of contraction (Blazevich et al., 2008). Onset was defined as the instant when the knee extensor torque exceeded baseline by 7.5 Nm (Blazevich et al., 2008) and all data were visually inspected to ensure correct onset.

Electromyography

Electromyography (EMG) from m. vastus lateralis (VL) and m. vastus medialis (VM) muscles were measured during the isometric contraction to quantify if changes in RFD were related to changes in neural drive. Following careful preparation of the skin (shaving and cleaning with ethanol), a pair of surface EMG electrodes (Blue sensor R-00-S/25, AMBU, Ballerup, Denmark) were placed at the thickest part of muscle belly (35 mm center-to-center interelectrode distance). The position of EMG electrodes were recorded in relation to specific bone marks and carefully replicated during both pre- and post-testing to ensure identical recording positions. The electrodes were connected to a wireless probe placed on the skin, which pre-amplified and transmitted the signal in real time to a PC-interface receiver (TeleMyo™ 2400T DTS, Noraxon Inc., Arizona, USA). All EMG sampling were recorded online at 1500 Hz, passed through a digital first-order high-pass filter with a 10 Hz cutoff, synchronized to the force signal and saved in EMG sampling software (MyoResearch XP, Noraxon Inc.). During the offline analysis, EMG data were filtered using a moving root mean square filter with a time constant of 50 ms (Robertson, 2004). From each trial, the rate of EMG rise (RER) was identified as the slope of the filtered EMG curve calculated in time periods of 0–30,

0–50, and 0–75 ms. EMG onset was initiated at 70 ms prior to muscle contraction onset to account for electromechanical delay (Aagaard et al., 2002) and 75 ms was chosen instead of 100 ms since previous research has shown a decrease in EMG amplitude following 80–100 ms (Aagaard et al., 2002).

To account for changes in coactivation, we furthermore collected EMG from the lateral (m. biceps femoris) and medial (m. semitendinosus) hamstrings collected and quantified as described above for VL and VM.

Statistical analysis

Following check for normality of distribution and tests of equal variance, data were expressed as mean ± SEM. ICC analysis was conducted using a large one-way analysis of variance (ANOVA). Differences in total volume load between contraction types were examined using Student's paired *t*-test and differences in total load between groups were examined with independent *t*-test. Regional differences in patellar tendon CSA at distal, mid, and proximal level were analyzed with a one-way ANOVA followed by Sidak post-hoc analysis. EMG data were log transformed (due to non-uniform variance) for statistical analysis purpose and presented as nontransformed mean ± SEM.

The effect of time (pre vs post), group (WHD vs PLA) and contraction mode (eccentric vs concentric) and their interactions on dependent variables (quadriceps CSA, patellar tendon CSA, MVC, RFD, normalized RFD, contractile impulse and RER) were assessed using a mixed-effect three-way ANOVA with repeated measures for time. The within-subject design (repeated measures on the same subject within contraction mode and time) was accounted for in the model by using subject, subject × contraction mode and subject × time as random effects. Linear comparisons were used to compare differences within and between individual conditions.

Correlations analysis on changes in quadriceps CSA, patellar tendon CSA and absolute quadriceps CSA, and patellar tendon CSA were made using a Pearson product-moment correlation analysis. Significance was set at an alpha level ≤ 0.05. All statistical analysis were performed using Stata (Stata v 11.2, StataCorp LP, College Station, Texas, USA) and all graphs were designed in GraphPad Prism (Version 5.0d, San Diego, California, USA).

Results

Baseline characteristics

There were no differences between the groups in anthropometric characteristics, quadriceps CSA and MVC (Table 2) before engaging in the training program. Combining all groups at pre-training the patellar tendon CSA was larger at the distal level (1.56 ± 0.05 cm^2) compared to the mid-level (1.35 ± 0.04 cm^2; $P < 0.01$), with no difference between distal and proximal levels (1.43 ± 0.04 cm^2) or mid and proximal levels.

Total volume load

The total volume load in the WHD group was 164 613 ± 6739 kg and 148 267 ± 5669 kg and in the PLA group 160 923 ± 11 978 kg and 146 124 ± 11 086 kg for the eccentric and concentric legs, respectively. In the WHD and the PLA group, the load for eccentric leg was 11.0 ± 0.8% and 10.3 ± 0.8% higher than the concentric leg, respectively ($P < 0.001$). There was no difference between the groups in neither total volume load nor in the load difference between the eccentric and concentric leg.

Quadriceps CSA

The hypertrophy pattern (comparing supplementation and contraction type) was similar at both the mid-level CSA and for ΣCSA with an overall time effect ($P < 0.001$, Fig. 2).

In the WHD group, the eccentric and concentric leg CSA increased by 8.3 ± 1.3% and 6.2 ± 1.4% at mid-level and by 5.8 ± 1.0% and 5.1 ± 0.7% for ΣCSA, respectively ($P < 0.001$), with no difference between contraction modes (Fig. 2). In the PLA group, the eccentric and concentric leg CSA increased by 2.7 ± 1.1% ($P < 0.01$) and 4.0 ± 1.0% ($P < 0.001$) at mid-level and by 2.2 ± 0.7% ($P < 0.01$) and 3.0 ± 0.8% ($P < 0.001$) for ΣCSA, respectively, with no difference between contraction modes (Fig. 2).

A group × time interaction was observed at both mid-level ($P < 0.01$) and for ΣCSA ($P < 0.001$) with a greater increase in the WHD group compared to the PLA group at mid-level (7.3 ± 1.0% vs 3.4 ± 0.8%) and for ΣCSA (5.4 ± 0.6% vs 2.6 ± 0.8%) independent of contraction type.

Table 2. Baseline characteristics of subjects in the whey protein group (WHD) and isoenergetic placebo group (PLA) at pre level. There were no differences between groups at pre level

	WHD ($n = 11$)		PLA ($n = 11$)	
Height (cm)	182.1 ± 2.5		181.0 ± 1.7	
Age (years)	23.7 ± 1.4		24.1 ± 0.9	
Body mass (kg)	78.3 ± 2.8		77.9 ± 2.2	
Fat percentage (%)	16.2 ± 1.4		15.7 ± 1.6	
Lean body mass (kg)	65.4 ± 1.6		65.1 ± 1.7	
	Eccentric	Concentric	Eccentric	Concentric
Quadriceps mid CSA (cm^2)	76.6 ± 2.7	7.78 ± 2.6	80.9 ± 2.6	79.4 ± 2.5
MVC (Nm)	280.3 ± 14.8	282.4 ± 15.5	297.9 ± 17.1	280.5 ± 19.1

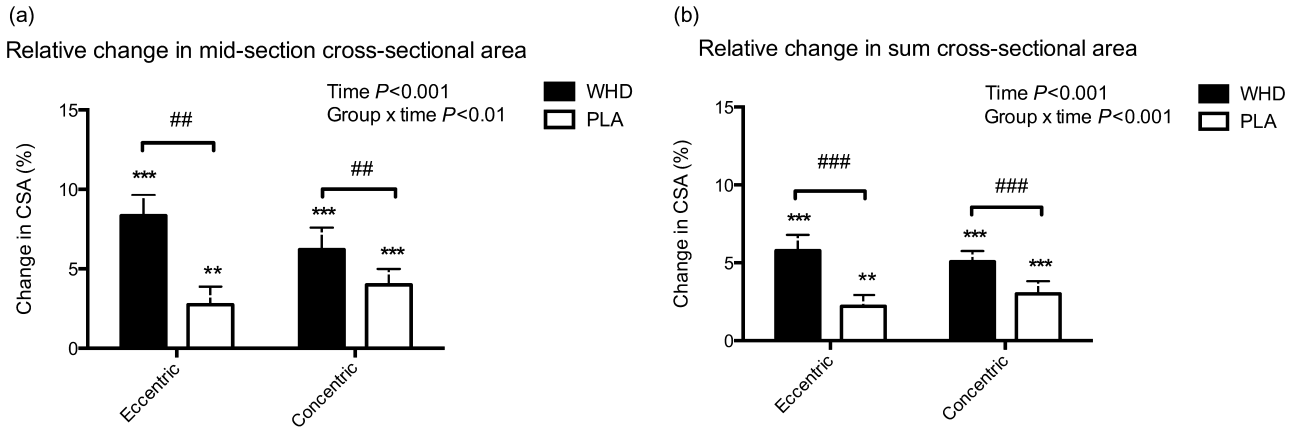

Fig. 2. Relative changes (%) in quadriceps muscle cross-sectional area (CSA) at femur mid-level (a) and the sum of distal, mid and proximal level (ΣCSA) (b) following 12 weeks of either eccentric or concentric resistance exercise with either whey protein (WHD) or placebo (PLA) supplementation. Data are shown as mean ± SEM. Time and group × time effects from ANOVA are shown in the upper right corner. Changes from pre-training are denoted by ** ($P < 0.01$) or *** ($P < 0.001$). Differences between groups are denoted by ## ($P < 0.01$) or ### ($P < 0.001$).

Patellar tendon CSA

At the proximal level, an overall effect of time was observed ($P < 0.001$). Accordingly, in the WHD group, patellar tendon CSA of the eccentric and concentric leg increased by 14.9 ± 4.8% and 14.9 ± 4.1%, respectively ($P < 0.001$, Fig. 3), with no effect of contraction mode. In the PLA group, the patellar tendon increased by 9.7 ± 5.1% ($P < 0.05$) in the eccentric leg, whereas no changes were observed for the concentric leg (6.5 ± 4.1%, $P = 0.126$, Fig. 3). For each group condition, there was an increase of 14.9 ± 3.1% ($P < 0.001$) and 8.1 ± 3.2% ($P < 0.05$) for WHD and PLA groups, respectively. There was a tendency toward a group × time interaction ($P = 0.054$), with a greater increase in the WHD group compared to the PLA group. This interaction became significant ($P = 0.042$) when using an analysis of covariance with the pre-training CSA as a covariate. No time-dependent changes were observed at the distal or mid-level.

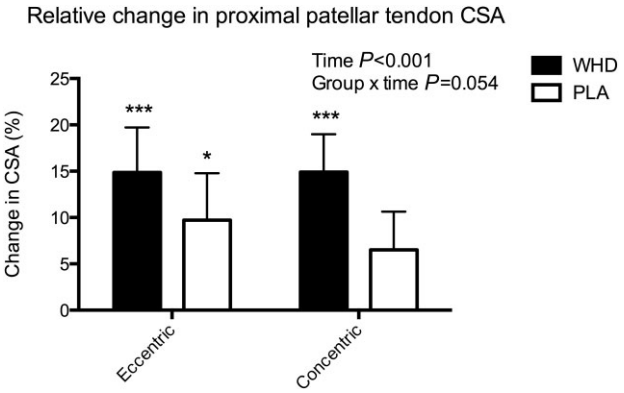

Fig. 3. Relative changes (%) in patellar tendon cross-sectional area (CSA) at the proximal level following 12 weeks of either eccentric or concentric resistance exercise with either whey protein (WHD) or placebo (PLA) supplementation. Data are shown as mean ± SEM. Time and group × time effects from ANOVA are shown in the upper right corner. Changes from pre are denoted by * ($P < 0.05$) or *** ($P < 0.001$).

Relationship between patellar tendon CSA, quadriceps CSA, and training load

Using pre-data only, there was a significant correlation between quadriceps ΣCSA and patellar tendon CSA at the proximal level ($r^2 = 0.18$, $P < 0.01$). Furthermore, when combining tendon CSA at distal, mid, and proximal levels (ΣCSA), there was a correlation between quadriceps ΣCSA and patellar tendon ΣCSA ($r^2 = 0.13$, $P < 0.05$). When adding post-data to the correlation, the significance of the association between quadriceps ΣCSA and patellar tendon at the proximal level ($r^2 = 0.18$, $P < 0.001$) and the patellar ΣCSA ($r^2 = 0.14$, $P < 0.001$) was further enhanced (Fig. 4). We found no correlations between changes in quadriceps muscle CSA and changes in patellar tendon CSA (at all three levels) in any of the four conditions or in pooled data.

Isometric strength performance and EMG

MVC increased by 12.4 ± 3.5% and 19.0 ± 6.4% ($P < 0.001$, Fig. 5 (a)) over time for WHD and CHO, respectively, with no differences between groups or contraction mode. $RFD_{30\ ms}$, $RFD_{50\ ms}$ and $RFD_{200\ ms}$ increased by 63.3 ± 31.3% ($P < 0.01$), 51.5 ± 26.8% ($P < 0.05$), and 12.0 ± 4.2% ($P < 0.01$), respectively (Fig. 5 (b)). Normalized RFD increased by 51.4 ± 18.1% ($P < 0.01$) at 1/6 of MVC with no changes at 1/2 or 2/3 of MVC (Fig. 5 (c)). Contractile impulse at 30 ms, 50 ms, 100 ms, and 200 ms increased by 39.6 ± 17.0% ($P < 0.01$), 50.5 ± 22.7% ($P < 0.01$), 48.4 ± 24.1% ($P < 0.05$) and 27.3 ± 12.7% ($P < 0.05$), respectively (Fig. 5 (d)). There were no contraction type or group interactions for RFD, normalized RFD, or contractile impulse.

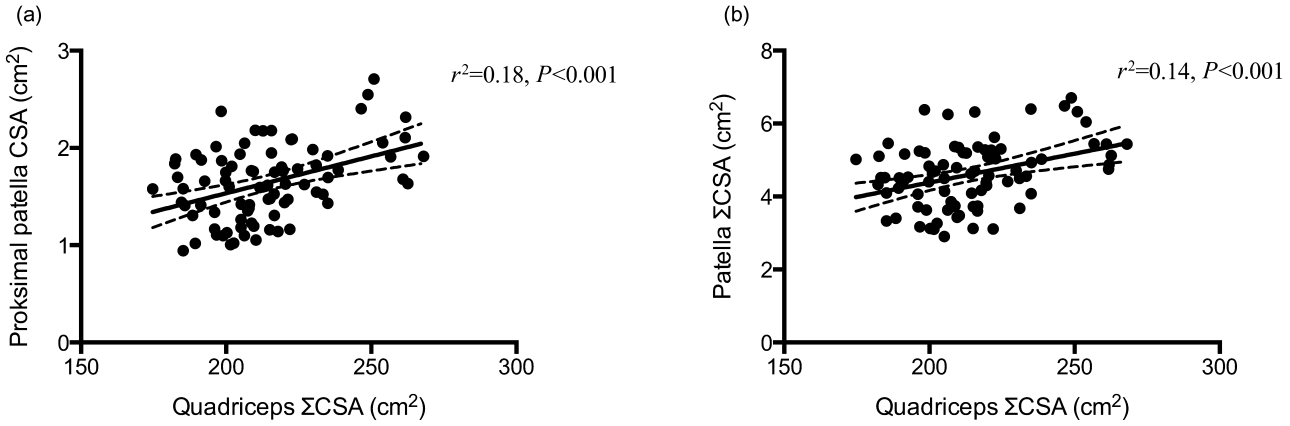

Fig. 4. Association between the sum of the distal, mid and proximal quadriceps cross-sectional area (Quadriceps ΣCSA, cm^2) and the proximal (a) or sum of the distal, mid, and proximal (patellar ΣCSA) (b) patellar tendon cross-sectional area (cm^2). Data from before and after training data are combined. Dashed lines indicate 95% confidence intervals. The level of association were in (a) $r^2 = 0.18$ and $P < 0.001$ and in (b) $r^2 = 0.14$ and $P < 0.001$.

The changes in RFD and contractile impulse there were not driven by changes in neural drive since no time effects (or interactions) from RER in VL or VM in neither of the selected time steps were observed (Fig. 6). Furthermore, there were no changes in coactivation of BF or ST (data not presented).

Discussion

The primary findings of this study were (a) that prolonged isotonic isolated eccentric and concentric exercise promoted tendon as well as muscle hypertrophy; (b) that training-induced hypertrophy of both tendon and muscle were augmented with a high-leucine whey protein hydrolysate supplement; and (c) that these effects were observed to be independent of contraction modality.

To our knowledge, this is the first study to employ a within-subject design to compare the effect of lower extremity isotonic eccentric vs concentric training on muscle and tendon hypertrophy, and, in addition to investigate the interaction of the two contraction modes combined with either a high-leucine whey protein hydrolysate supplement or an isoenergetic placebo supplement.

By this comparative approach, for one thing, we were able to investigate the effects of divergent dietary supplementation types on muscle and tendon growth with resistance training *per se*.

Resistance training-induced changes in tendon and muscle morphology is augmented by provision of high-leucine whey protein hydrolysate

An intriguing and novel finding from our study relates to the observation that patellar tendon hypertrophy can be augmented with resistance training combined with whey protein hydrolysate supplementation. Only few previous studies have looked into this aspect of tendon adaptations and results are at this point somewhat equivocal. Accordingly, increased tendon collagen synthesis, has previously been observed following endurance-type knee kicking exercise in humans (Miller et al., 2005) and a tendency for increased muscle collagen synthesis has been observed (Dideriksen et al., 2011) following resistance exercise when subjects consumed an amino acid supplement. Oppositely, other previous studies have not been able to demonstrate any effect of amino acid supplementation on tendon (Babraj et al., 2005) or muscle collagen synthesis (Holm et al., 2010) under conditions of rest and resistance exercise, respectively. However, to our knowledge, no previous studies on humans have investigated the combination of resistance training and high-leucine whey protein hydrolysate ingestion on tendon collagen synthesis. In this regard, it is interesting that recent observations on rodents indicate that the amino acid, leucine, could be of specific importance for stimulating collagen synthesis (Barbosa et al., 2012). Furthermore, the type of feeding, bolus (Dideriksen et al., 2011) vs repeated small dosages (Holm et al., 2010) may affect collagen synthesis differently, with a bolus-type feeding required for maximal stimulation of collagen synthesis (Dideriksen et al., 2011). Considering the high leucine content in our whey protein supplement and the bolus-type feeding, this may have exerted stimulatory effect on collagen synthesis of the patellar tendon, which in combination with a high-sample size, was sufficient to enable detectable change in tendon hypertrophy. Furthermore, in accordance with previous longitudinal studies (Kongsgaard et al., 2007; Seynnes et al., 2009; Carroll et al., 2011), we only observed a regional dependent increase in patellar tendon CSA following resistance training *per se*, which may be explained by the greater bone-tendon compression at the osteotendinous junction sites potentially stimulating collagen synthesis (Kongsgaard et al., 2007). In relation to patellar tendon hypertrophy, we recognize that the presence of patellar tendinitis ("jumpers knee")

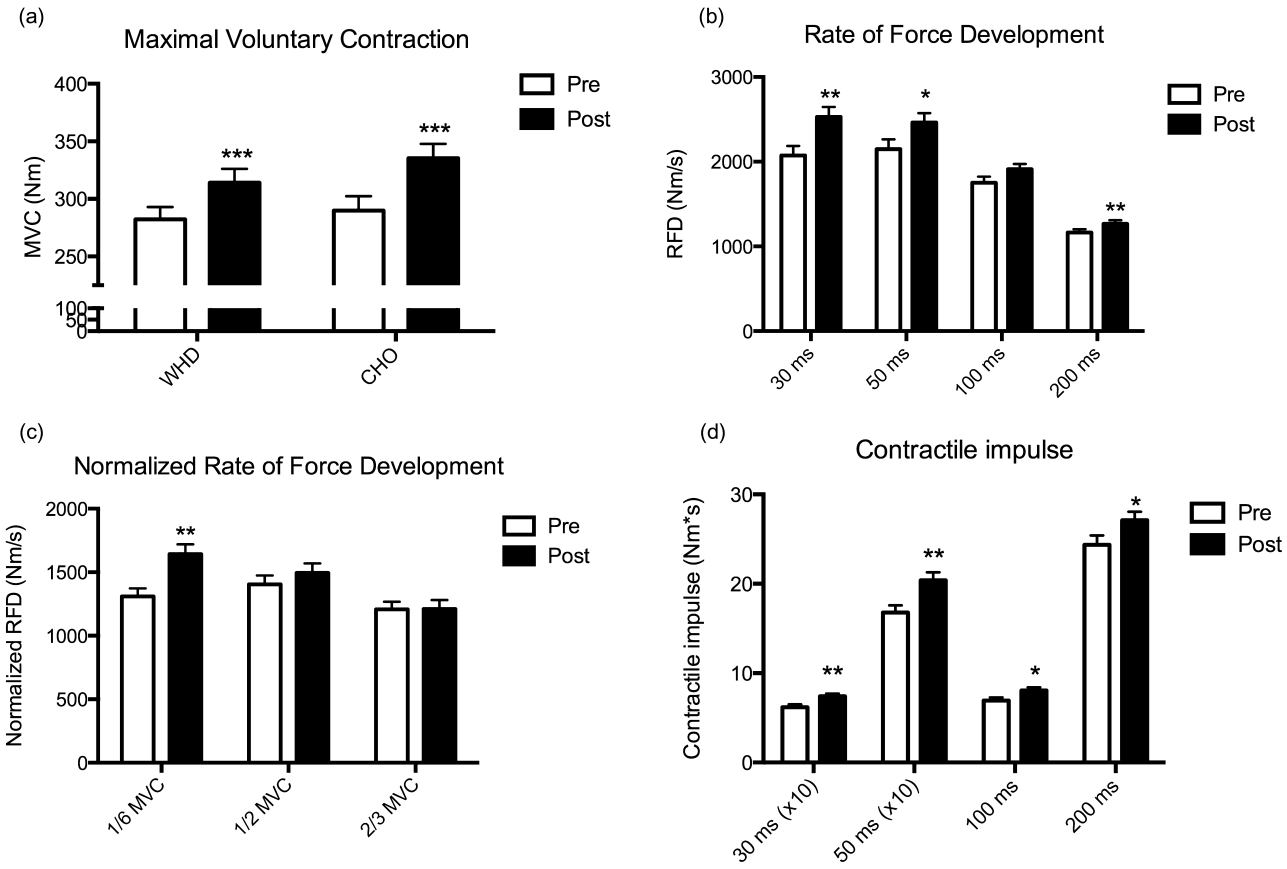

Fig. 5. Isometric maximal voluntary contraction [MVC (Nm)] (a), rate of force development [RFD (Nm/s)] (b), normalized RFD (Nm/s) (c) and contractile impulse (Nm*s) (d) before and after 12 weeks of either eccentric or concentric resistance exercise with either whey protein or placebo supplementation. Data are shown as mean ± SEM. For MVC data were shown according to supplementation, whereas RFD, normalized RFD, and contractile impulse data were pooled for both contraction modes and supplementation. Significant difference change from pre-exercise are denoted by * ($P < 0.05$), ** ($P < 0.01$), or *** ($P < 0.001$).

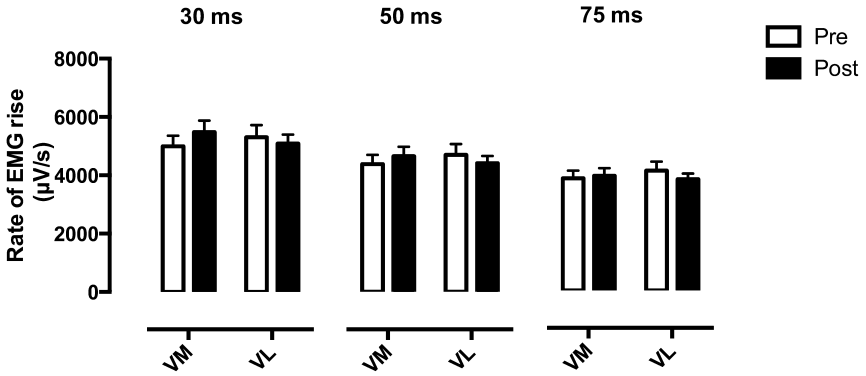

Fig. 6. Rate of EMG rise [RER (µV/s)] from vastus medialis (VM) and vastus lateralis (VL) before and after 12 weeks of either eccentric or concentric resistance exercise with either whey protein or placebo supplementation. Data are shown as mean ± SEM. There were no changes in neither of the measured variables following training and since no interactions were observed data from both contraction modes and supplementation types are shown as pooled data.

may cause a "false" increase in tendon CSA. While some subjects in the present study did experience patellar tendon soreness, this occurred during weeks 3–5 and subsequently resolved in the following weeks, presumably not influencing the CSA measurement following the 12 weeks of training. Moreover, we observed no association between previous complaint of tendon soreness and changes in CSA.

In regards to the effect of high-leucine whey protein hydrolysate supplementation + resistance training, we observed that knee extensor hypertrophy from isotonic eccentric as well as concentric training was augmented

with provision of a high-leucine whey protein hydrolysate supplement. We did observe an increase in quadriceps CSA in the isoenergetic placebo group, albeit to a lesser extent compared to the WHD group. The observed magnitudes of relative increases in muscle CSA is comparable to previous studies, applying CRE training both with (Esmarck et al., 2001; Hartman et al., 2007; Hulmi et al., 2009) and without (Aagaard et al., 2001; Farup et al., 2012) timed protein intake and suggest that both contraction modalities can induce substantial muscle hypertrophy. However, most studies do not report the amino acid and peptide profile of the protein source used in the study potentially limiting exact comparison to the protein product used in the present study (see Table 1 for profile). Both leucine content and peptide profile may affect the anabolic response following ingestion (Hulmi et al., 2010; Breen & Churchward-Venne, 2012) and differences between protein sources utilized may in part explain why some studies (e.g. Verdijk et al., 2009) did not observe any interaction between training and supplementation and furthermore highlighting the importance of a detailed description of the amino acid and peptide profile.

Resistance training-induced changes in tendon and muscle morphology are not influenced by divergent contraction mode

The other issue our comparative design allowed us to address, was the issue of whether a specific contraction mode (i.e. isolated eccentric vs isolated concentric exercise training), when performed isotonically, was superior in augmenting muscle and tendon growth. In this regard, unlike most previously applied models that have utilized isokinetic exercise mode, it was attempted to approach the exercise isotonically, as it is often genuinely practiced. Furthermore, by choosing a paired design for contraction mode (i.e. unilateral eccentric and concentric exercise with contralateral legs), we minimized the potential influence of, e.g. nutrient intake and physical activity during the training period, and furthermore, limited any potential influence from systemic factors. By this approach, in contrast to some (Higbie et al., 1996; Hortobagyi et al., 1996; Vikne et al., 2006) but not other (Blazevich et al., 2007; Reeves et al., 2009; Moore et al., 2012) earlier studies, we find that isolated isotonic eccentric and concentric exercise training seem equally capable of inducing muscle hypertrophy. In this regard, we acknowledge that we employed a nonwork-matched design. We did this to allow us to observe changes from exercise training as it is more commonly practiced. Still, by this approach, our results are in line with previous studies suggesting no superiority of eccentric exercise contraction mode in promoting muscle hypertrophy.

Another possible explanation for the lack of detectable difference in muscle hypertrophy with divergent exercise contraction mode may relate to the rather high volume of work in our exercise protocol. Whereas this was chosen to assure promotion of muscle hypertrophy (while only utilizing one lower extremity exercise), there is the possibility that it may have created a similar state of fatigue in the two conditions. In this regard, data from a meta-analysis indicates that the rate of increase in CSA may declines at higher training volumes suggesting that at some level, further increase in total work will not lead to further increases in CSA (Wernbom et al., 2007). Thus, it seems that muscle hypertrophy is less dependent on contraction mode than on training volume.

As for the influence of resistance exercise contraction mode, on tendon hypertrophy, in line with the findings for muscle hypertrophy, we found no difference between the two contraction modes, once again suggesting that load (intensity) and/or volume rather than specific contraction modes are responsible for tendon-induced hypertrophy. In this regard, in a previous study, a greater effect on tendon hypertrophy from heavy compared to lighter loading was observed (Kongsgaard et al., 2007), although, it should be emphasized that the difference in loading intensity applied in this study (i.e. approximately 70% vs 25–30%) was much greater compared to the present study. Furthermore, results from Holm et al. (2010), on collagen synthesis following heavy vs light resistance exercise, showed no difference in collagen synthesis response between the divergent loading intensity conditions, suggesting that total work may be a stronger driver than loading intensity. In line with these findings, our current results suggest that similar to muscle tissue, total loading (and not contraction mode) may be the primary driving factor for tendon hypertrophy.

Effects of dietary and exercise modality manipulation on muscle strength measures

In regards to adaptations in strength gains, isometric strength measures generally increased quite similarly regardless of resistance exercise contraction mode performed during training (Fig. 5). There were no effects of dietary supplementation on neither of the different strength parameters despite the observed difference in muscle hypertrophy. Such lack of coherence between training-induced changes in hypertrophy and strength have been observed previously (Andersen et al., 2005; Hartman et al., 2007; Hulmi et al., 2009; Mitchell et al., 2012) and is in part explained by the influence exerted by complex neuromuscular interactions also affecting muscle strength (Folland & Williams, 2007). Overall, our results on strength measures are similar to previous findings using either conventional resistance training (Farup et al., 2012), eccentric training, or concentric training (Blazevich et al., 2008; Moore et al., 2012). Accordingly, we observed that both eccentric and concentric training are capable of increasing not only maximal strength but also RFD and contractile impulse. However, these changes were not accompanied by an

increase in initial neural drive as quantified by RER. This is in agreement with results from Blazevich et al. (2008) showing no changes in initial neural drive during an isometric contraction following isolated eccentric or concentric exercise. The lack of change in RER suggests that the increase in RFD and contractile impulse is primarily driven by the increase in MVC. This was confirmed by using the changes in MVC as a covariate in the statistical analysis, which resulted in a cancellation of the changes in RFD and contractile impulse.

In summary, we observed that resistance training-induced tendon, as well as muscle hypertrophy following 12 weeks of resistance training *per se*, was augmented by high-leucine whey protein hydrolysate supplementation compared to isoenergetic placebo supplementation. These effects of high-leucine whey protein hydrolysate supplementation on muscle and tendon hypertrophy were not observed to differ with divergent contraction mode performed during exercise training.

Perspectives

The current study provides several important observations in relation to adaptations on both muscle and tendon tissue following resistance exercise training. Firstly, our results suggest that muscle hypertrophy can be induced independent of specific contraction modes when using isotonic training equipment. Moreover, we showed that the effect on muscle hypertrophy is augmented with a high-leucine whey protein hydrolysate supplementation supporting previous studies on CRE training (Esmarck et al., 2001; Andersen et al., 2005; Hartman et al., 2007; Hulmi et al., 2009). We therefore propose that the mechanisms driving muscle protein synthesis and ultimately muscle hypertrophy is less dependent on specific muscle contraction modes per se, whereas timed protein ingestion is a strong determinant for inducing muscle hypertrophy. A second, however also important, observation was the potential interaction between high-leucine whey protein hydrolysate and resistance exercise on tendon hypertrophy. This could have important clinical implications since augmented tendon hypertrophy may lower the mechanical stress (thereby also strain) on the tendon during exercise and potentially assist in tendon rehabilitation following injury. Finally, our correlation analysis supported the association between muscle and tendon CSA and thereby, the coherency between the forces imposed on tendon tissue and the tendon CSA.

Key words: strength training, patellar tendon, eccentric training, concentric training, rate of force development, isotonic.

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