Review Article

BIOMEDICAL
Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2022.46.007312

Effect of Nutritional Intervention on the Temporal Dynamics of Muscle Strength Adaptation

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ARTICLE INFO

Received: September 08, 2022

Published: September 15, 2022

Citation: Robert Gaudin, Jan Dirk Raguse, Sophie Krause, Jennifer Mumm, Yvonne Motzkus, et al. Quality of Life and Psychological Evaluation of Patients After Anaplastology. Biomed J Sci & Tech Res 46(2)-2022. BJSTR. MS.ID.007311.

Keywords: Supplement; Protein; Whey; Leucine; Creatine; HMB; Hydroxy Methylbutyric Acid; Temporal Dynamics; Time-Related Adaptive Response; Muscle Adaptation; Strength Adaptation; Resistance Training; Nutritional Response; Muscle Strength

ABSTRACT

The generally accepted modus operandi for stimulating muscle strength adaptation is high-magnitude resistance training which is facilitated by protein and with the addition of augmented exogenous protein intake this outcome is potentiated. The aforementioned protocol has been observed in many studies over time periods (up to 12 weeks) however; very few longitudinal studies have examined the temporal dynamics of muscle strength adaptation throughout the entire period. These data could prove vital in constructing training and rehabilitation programs for both athletes and non-athletes. The objective of this review was to establish whether high-magnitude training with the addition of nutritional supplementation results in enhanced temporal adaptation dynamics and at what point these adaptations are significant. The searches were achieved utilising PubMed, Google Scholar, Medline, ScienceDirect, Wiley Online and SPORTS. Discuss databases. Of the inclusion criteria a total 362 participants from 11 studies were included in the review and concluded that the mean time point for muscle adaption was ~6.7-weeks. With the results indicating that adaptation to high-magnitude resistance training occurred at each time-point (up to and including 10, 12 and 24-weeks) for the training only groups of each study (placebo), this was equivalent to the supplement intervention group. While, both groups evidenced adaptation only ~27% showed significance between the placebo and intervention groups.

These findings are contrary to the known paradigm that supplements enhance muscle protein synthesis thus recovery and subsequent adaptation. However, there are considerations regarding the protocols used in the studies reviewed including dietary standardization that may have impacted the results. Notwithstanding, the results do indicate that supplements may enhance the effects of high-magnitude training and that this could have an impact on temporal adaptation dynamics leading to augmented muscle strength increases at an earlier stage in a training cycle than the current paradigm dictates. This could pose problems for other associated tissues such as tendinous tissue, as a differential in adaptation between muscles and tendons could cause non-uniformities within the muscle-tendon-unit and potentially lead to tendinopathy. Consequently, it may be prudent to investigate the temporal dynamics of muscle and tendon adaptation with a supplement intervention.

Introduction

Muscular adaptation is determined by parameters of mechanical loading, including intensity, load, and duration (Hickson, et al. [1,2]) and adequate nutritional support (Cermak, et al. [3]). Notwithstanding, the primary stimuli appear to be intensity and duration coupled with sufficient resistance (Schuenke, et al. [4]) and variants of these protocols are used throughout the world by professional and recreational athletes to promote muscle size and strength. Based on the classical overload principle a certain threshold needs to be exceeded in order to cause the optimum improvements in muscle strength, accordingly moderate to high mechanical loading has been proposed as the main stimuli to initiate muscle hypertrophy and increase strength adaptation (Hakkinen, et al. [5]). In general, it has been widely acknowledged that the initial phases of training that induce muscle strength improvements are predominantly redirected to the enhanced neuromuscular components (Carroll, et al. [2,6]), whereas morphological changes (hypertrophy) do not occur in muscle tissue until after six to eight weeks of high-magnitude resistance training (Verdijk, et al. [7]). The neurological adaptations that initiate and later augment muscular strength adaptation occurs as a resultant factor of mechanical resistance training and leads to significant increases in strength within the first two-weeks of training (Aagaard, et al. [8]). However, the specific mechanisms involved are still being debated and investigated. It has been postulated that the agonist skeletal muscle activation during high-magnitude mechanical loading could be as a result of augmented motor unit recruitment or firing frequency. While it has been shown that motor unit activation can be slightly changed with mechanical loading training protocols (Patten, et al. [9]) the study of motor units pre- and -post mechanical loading interventions appear to follow the size principle regardless of stimuli i.e., isometric or dynamic contractions [10].

Nevertheless, although the size principle appears to be conserved post training the absolute force that a specific motor unit is recruited depends on the augmented contractile force and contraction time of low-threshold units post training (Aagaard, et al. [11]). Another consideration that has been shown to impact neuromuscular adaptation is the application of a particular training protocol, explosive or steady state muscular contractions [9] evidenced that contraction type can determine neuromuscular response with progressive maximal contractions eliciting greater adaptations than rapid explosive contractions. The initial increase in neuromuscular adaptation enables larger loads and greater intensity to be achieved within the parameters of the training protocol therefore, the resultant factor will be further augmented adaptation leading to morphological changes (Duchateau, et al. [12]). Morphological changes are initiated to protect the skeletal muscular system from damage caused by external factors i.e., high-magnitude mechanical loading (to maintain homeostatic balance) (Haun, et al. [13,14]). The morphological change in response to high-magnitude mechanical loading results in enlargement of the muscle fibres, hypertrophy. The increase in the cross- sectional area (CSA) of skeletal muscle augments the strength of the muscle, as the CSA of a muscle is directly proportional to the force of the muscle. The morphological adaptation of muscle tissue is initially stimulated by mechanical stress which leads to metabolic stress (fatigue driven), initiating a plethora of other factors including hormonal changes; testosterone, insulin-like growth factor-1 (IGF-1), insulin fluctuations; nutritional intake; protein, carbohydrates, electrolytes; recovery and timing of feeding to stimulate muscle adaptation, all these factors evoke adaptation [15].

High-magnitude mechanical loading causes mechanical stress during the concentric and specifically the eccentric phase of skeletal muscle contraction creating a greater hypertrophic response (Lixandrao, et al. [16]). Where eccentric contractions are challenging the sarcomere, the length is compromised and elongated beyond myofilament overlap, the tension augments and the actin-myosin cross-bridge integrity becomes compromised resulting in micro tears [17,18]. Continued contraction additionally damages the integrity of the sarcomere resulting in augmented calcium release and leads to damage to the sarcoplasmic reticulum leading to localised oedema and soreness as a result of inflammation. To elucidate further mechanical stress coupled with metabolic fatigue leads to localised metabolic stress resulting in increased activation of mechanosensitive calcium channels, intracellular enzymes and second messengers. IGF-1 is also secreted from the muscle cells triggering signalling cascades resulting in muscle protein synthesis (MPS) (Yang, et al. [19-23]). The increase in MPS stimulates additional molecular mechanisms that augment sarcomeres and myofibrils contractile elements size expanding the extracellular matrix to support growth/hypertrophy (Haun, et al. [13]). Regardless that this study is concentrating on the examination of skeletal muscle adaptation via high-magnitude mechanical loading (predominantly strength training protocols), heavy resistance low-volume or light resistance and high-volume training effects strength adaptation to some degree, and a subsequent change in fibre type size (Campos, et al. [24-27,13]). There is evidence that resistance training elicits a greater effect on Type II muscle fibre with satellite cell proliferation and differentiation augmenting (Kadi, et al. [25,28]). Together with sarcoplasmic expansion and coordinated up-regulation of sarcoplasmic proteins involved in glycolysis and other metabolic processes related to ATP generation. This suggests that Type II muscle fibres (fast twitch fibres generating more force) can adapt significantly to resistance training by increasing their size (Verdijk, et al. [29]).

To facilitate the mechanisms of adaptation post mechanical stimuli adequate nutrition is essential, with specific attention to protein consumption (Esmarck, et al. [30-36]). A positive nitrogen balance provided by protein feeding is required to ensure remodelling of contractile machinery leading to hypertrophy (McGlory, et al. [37]). Nutrition is therefore a fundamental external element that can be manipulated to ensure a positive nitrogen balance is maintained post training to facilitate MPS, (Andrews, et al. [14]). The protocol for pre-training and post-training feeding is well documented (Berardi, et al. [33,38]) and there are a plethora of peer-reviewed papers and scientific publications providing robust paradigms for creating an environment for muscular adaptation (Hickson, et al. [1,30,39]). Many of these studies concentrate their attention on high-magnitude mechanical loading followed by protein feeding resulting in an augmentation of MPS and thus, over time, muscle hypertrophy (Cermak, et al. [3,39]). It has been established that to augment the adaptation of skeletal muscle tissue post resistance training an increase in protein consumption is required and in particular the amino acid (AA) leucine and supplements derived from leucine i.e., hydroxy methylbutyric acid (HMB) have been shown to be effective [40]. Leucine functions directly with mammalian target of rapamycin (mTOR), during resistance training mTOR activation is inhibited by AMP Activated protein kinase (APMK) as AA's become available for energy metabolism. However, during recovery AMPK activation is decreased and mTOR reaches peak activity and as mTOR is known as an important signalling molecule involved in muscle hypertrophy it is important to potentiate its activation [41,42].

With the addition of protein to the habitual diet to enhance the anabolic environment post training other supplements have been determined to be effective. Although, there are a plethora of novel supplements available few supplements have been researched with more veracity than protein and creatine. These supplements have proven to have ergogenic characteristics and while the scientific evidence is esoteric, the general principles are known by the public therefore it would be prudent to ensure the validity of these claims and ensure that the public are utilising these supplements correctly. Creatine is unquestionably one of the most researched supplements of the past 30-years, the efficacy of creatine is well documented; it augments phosphocreatine (PCr) energy stores; augmenting PCr resynthesis; and reducing muscle damage through buffering the increases in lactate and hydrogen ions. However, there is no clear evidence that creatine directly enhances MPS and thus muscle strength adaptation however, it does impact performance positively by enabling greater force production. This creates an optimal environment to work/train with higher intensity over a short period of time, with this maximal intensity damage to the musculature is enhanced resulting in adaptation. The augmented response to training and the congruent adaptation results in hypertrophy and therefore an increase in the CSA of the muscle. (Wilder, et al. [43-50]).

With the addition of the traditional aforementioned supplements there has been a surge in research into additional supplements that will enhance the recovery and adaptation post mechanical loading protocols. Metabolites of leucine including Hydroxy methylbutyrate (HMB) and Hydroxyisocaproic Acid (HICA) are being increasingly used as supplements to augment the impact of leucine on the mTOR pathways to enhance MPS (Gallagher, et al. [51-54]). With HMB purporting to have anticatabolic actions acting antagonistically against the effects of acute bouts of resistance training where there is an increased breakdown of protein. HMB partly prevents this exercise induced proteolysis thus, causing assuaged muscle damage and therefore recovery becomes more expedient and gains in MPS follow (Phillips, et al. [19,20]). These effects have been observed in both young and elderly adults (Nissen, et al. [55]). There is substantial evidence that supplements augment skeletal muscle adaptation as a result of high-magnitude mechanical loading however, there is little evidence of the rate of adaptation. The accepted and established paradigm is that neurological changes occur within the first 2-3 weeks of training and morphological adaptation does not initiate transpire until after that period. Moreover, there is little known regarding the effects of the addition of supplements to in the equation, will there be a direct correlation with known studies evidencing an augmented response to supplement ingestion over a 12-week period when applied to a resistance training protocol or will this increase occur more expediently after 2-3 weeks rather than 6-8 weeks (Gabrie, et. [56,57]).

Aims of the Review

Research indicates that there are many parameters influencing adaptation time induced by mechanical loading, including intensity, load, duration and enhanced neural drive (which has an immediate response) (Hickson, et al. [1,2]). However, morphological changes do not occur in muscle tissue until after three to four weeks of high-magnitude resistance training. To elucidate further, neural adaptation increases the plasticity of the force generating capacity of the neuromuscular system which leads to enhanced muscle strength leading to greater adaptations (Fimland, et al. [2,58]). The inclusion of an enhanced nutritional regime with the addition of supplements, including but not limited to whey protein, leucine, HMB and creatine to augment the recovery process caused by mechanical stress (Vandenberghe, et al. [59,60,30,31,46,7,61,54]) could impact the temporal dynamics of strength adaptation. The rationale of the review therefore is to evaluate available peer-reviewed studies for specific criteria relating to or including temporal dynamics (time-course changes) during strength training protocols over a period of at least 6-weeks (max. 12-weeks) with the addition of a nutritional/supplement intervention. With the aim of the review to elucidate current paradigms with special attention on potential gaps in current research. For the purpose of this study, the term 'supplement' will be used to refer to any oral product designed to augment the effects of resistance/strength-training exercises i.e., protein, leucine, HMB and creatine. There are cornucopia of studies relating to resistance training protocols to enhance muscle adaptation including studies that comprise a supplement element. However, these studies predominantly use pre- and post-intervention data to evidence adaptation, this review will use only data given from time-based adaptations to resistance training with a supplement intervention included (with a minimum of pre-, mid- and post-adaptation data).

Examining the temporal dynamics of muscular strength adaptation is vital as the information provided from researched based evidence could be used to provide a protocol for strength and recovery training programs. As discussed previously there is a convention regarding strength adaptation over a 10-week plus intervention, the evidence that adaptation does occur as a result of resistance training is overwhelming. There is also evidence that supplementation augments this adaptation however, at what time-point does the supplement augment the conventional muscle adaptation as this change could impact a training schedule. As supplements are utilised as ergogenic aids, with the paradigm that they elicit enhanced performance via maximising muscular adaptation as a result of training it is essential that the parameters are known. Paradoxically, using supplements to augment the recovery process thus potentiate muscle adaptation via resistance training could have adverse consequences. There could be imbalances in adaptation between muscle and tendon tissue thus causing disparities within the muscle-tendon-unit (MTU) (Mersmann, et al. [21]) this could potentially cause tendinopathy. Naturally, there are also implications for the development of training protocols to be considered for sports scientists, coaches etc., to use with their athletes. Regular adjustments will need to be assessed if the athlete has added supplements to their diet, ensuring that adequate stimuli is maintained to continue with training progression [55,62]).

Therefore, the objectives of this review are to find evidence of resistance training protocols that elicit strength adaptations over a time-course when a supplement intervention is added and to compare these results to a control group to evidence phases of adaptation. The resultant evidence may indicate a differential between the temporal dynamics of resistance training with and without a supplement intervention. Therefore, if there is found to be a correlation between supplement intervention and an increase in temporal dynamic adaptation the type of supplement and dosage will be exposed.

Materials and Method

The review was conducted in accordance with the search strategy guidelines using the criteria of the Preferred Reporting Items for Systemic Reviews and Meta-Analysis. The review was conducted via electronic databases search for peer-reviewed papers examining temporal dynamics of muscle strength adaptations resulting from supplement ingestion. With the term ‘supplement’ referring to oral consumption of a nutrient purported to augment the adaptation of muscle tissue as a result of mechanical stimuli [55]. The electronic searches were limited to English language citations published in PubMed database and Google Scholar from 1980 onward DISCOVERY resources at London South Bank University were also utilised for the initial citation and abstract searches. Additional refined searches were conducted to also include conference papers using EBSCO host which included the data bases Medline, ScienceDirect, Wiley Online and SPORTS Discuss. A combination of the words and phrases associated with the subject matter were used in the search; ‘muscle adaptation’, ‘strength training’, ‘time-course adaptations’, ‘temporal dynamics’, ‘resistance training’, ‘nutritional response’, ‘muscle strength’, ‘HMB Hydroxy Methylbutyrate Acid and adaptation’, ‘leucine and strength adaptation’, ‘protein and muscle adaptation’, Creatine and muscle strength’, ‘creatine and performance over time’, ‘supplements and muscle adaptation’. Further references were sourced through manual crosschecking of peer-reviewed papers that pertained to the relevant search criteria ensuring absolute saturation of related papers.

Primary citations and abstracts were searched for the following criteria and peer-reviewed papers were included therein:

a) Studies published in English

b) Randomised controlled or controlled trials

c) Studies containing a nutritional intervention related to augmenting strength increases

d) Studies pertaining to resistance training where the primary aim was to increase muscle strength via training frequencies of more than twice weekly

e) Studies which had a duration of no less than 6-weeks

f) Studies measuring muscle strength in terms of 1 maximal repetition (1RM) or maximal voluntary contraction (MVC) pre-intervention, at least once during intervention and at the end of the intervention

g) A placebo control administered

h) Peer-reviewed papers post 1980. The studies included in the final review contained all the search criteria idiosyncrasies.

Results

Initially the databased search process yielded 410 studies with three studies identified through other sources leading to 413 studies after duplicates were removed. Thereafter, abstracts were read to ensure the relevance to the review, this led to the exclusion of 347 studies. The remaining 51 studies were fully read and examined in miniscule detail, which led to identification of a further 20 papers leading to 71 studies. Of the 71 studies examined 60 were excluded while 11 matched the criteria genus. Many of the studies were excluded due to the frequency of measurements taken. The vast majority of the studies examined only the measurements before and after the intervention, heralding interesting results but not the results required for the review. Figure 1. represents evidence of the search process with the PRISMA search flow diagram. (Table 1).

summaries each study. The details of the 11 peer-reviewed papers include in the review indicate that of the total 362 participants ~66% were male adults and ~34% were female adults with an age ranged between 18-93 years. Of the studies examined ~64% of the studies recruited exclusively male participants while ~27% utilised both genders with the remaining ~9% devoted to female participants. Regarding intervention duration, ~90% (n=10) were over 10-weeks with only one study lasting less that 10-weeks. However, the study lasting 6-weeks had measurements taken every 10-days for 40-days and then again at 6-weeks producing interesting data. The reviews characteristics pertained to a subject group that predominantly abstained from resistance training activities with ~73% of the studies including ~67% of the total participants. Only 27% of the studies reviewed used participants that used resistance training activities. A similar trend was established for the age of the participants with studies containing older adults comprising of ~64% of the total. With only one study recruiting sedentary women only between the ages of 19-22 years and three using trained individuals between 18-39 years.

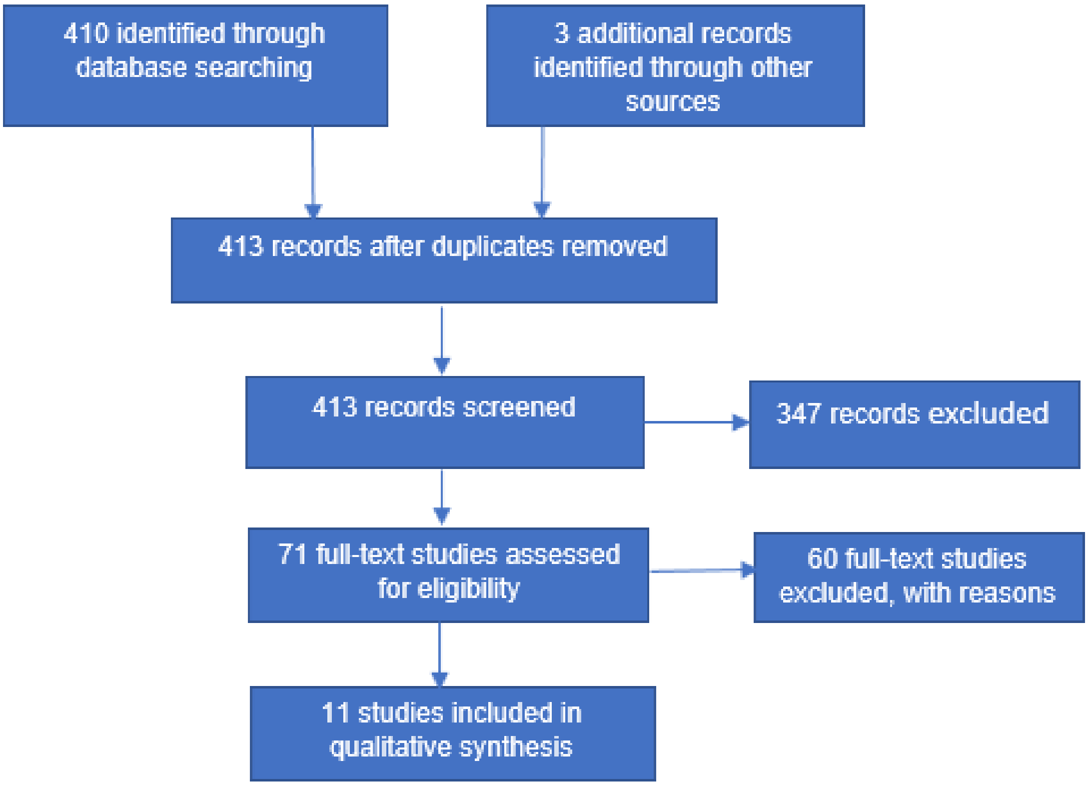

Figure 1: PRISMA search flow diagram (PRISMA; Moher et al., 2009).

Table 1: Brief descriptions of each study.

Title And Year	Participants	Type of Supplement Intervention	Intervention Duration	Muscle Groups Measured	Training Programme Performed	Testing Time-Course	Results
Timing of postexercise protein intake is important for muscle hypertrophy with resistance training in elderly humans. (Esmarck., 2001).	Participants 13 Men; - Age 74 ± 1 years	Protein supplement 10g immediately after training for group 1 (PO) and a protein supplement 2h post exercise for group 2 (P2). 4-day self-report food records.	12wks of 3 resistance training sessions per week.	M. Quadriceps. Muscle strength was determined using dynamic training strength (5RM) and isokinetic strength measurements	The resistance training consisted of three different concentric strength exercises: leg press, latissimus dorsi pulldown and knee extension. The load for the leg-exercises increased from 20 repetition maximum (RM) to 12 RM during the first 6 weeks (10–12 repetitions, 3–4 sets), and during the last 6 weeks it remained at 8 RM (8 repetitions, 3–5 sets)	0 - start, 6wks and 12wks	Dynamic training strength at 5 RM results increased for both groups. Isokinetic strength increased at both velocities (60 and 180 deg) for PO but not with sig for P2. Differences between P0 and P2 were observed only in the isolated non-trained isokinetic knee extension. In group P0 5 RM, and isokinetic 60 and 180 deg strength increased (P<0.05) 47 ± 4, 24 ± 9 and 21 ± 5 %, respectively at 0, 6 and 12wks, with training but for P2 there was no significance. No significant difference in the relative increase in strength was observed between P0 and P2 for any measurement. Thus, evidencing that there is an initial response but it is independent of the intervention.
The effects of protein and amino acid supplementation on performance and training adaptations during ten weeks of resistance training. (Kerksick et al., 2006).	36 (resistance trained male adults) mean age of 31.0 +-SD8.0. 15n whey + BCAA + L-glutamine (WBG); 15n whey protein casein (WC); and 11n control	Whey protein BCAA + glutamine (48g total protein) and whey protein with casein (total protein 48g). 4-days dietary record and no other supplements taken.	10wks of resistance training with 4 sessions per week.	Chest and legs. 1 RM measurements taken	Resistance training program 4 workouts, per week (2-upper & 2-lower) reaching muscular failure at the last rep of each set for a duration of 10wks.	0 (start), 5wks and 10wks	Significant increases over time, with no group differences found, indicating positive adaptations to the resistance training program.

The effects of 12 weeks of beta-hydroxy-beta-methylbutyrate free acid supplementation on muscle mass, strength, and power in resistance-trained individuals: a randomized, double-blind, placebo-controlled study. (Wilson et al., 2014).	20 resistance trained male adults aged 21.6 +- 0.5 years.	11n supplement group 3g HMB-FA divided equally into three servings. 9n placebo group. 2-weeks prior and during study special diet 25%p, 50%c and 25%f.	Total 12wks. Initial phase 1, 8wks resistance training program 3x per week. Phase 2 5x per week overreaching cycle for 2 weeks and phase 3, tapered training volume.	Measured 1-RM testing for the Back squat, bench press and deadlift and total strength.	Phase 1 undulating periodized resistance-training program (modified from Kraemer et al. (2009). The overreach weeks are of increased to 5 sessions per week plus Wingate and power testing sessions.	0 (start) 4wks, 8wks then 12wks	Total strength increases over the 12-week study were 77.1 ± 18.4 kg in the HMB-FA-supplemented participants. Mean total strength also demonstrated that the HMB-FA supplementation group was significantly greater at 4, 8, and 12 weeks during the periodized resistance-training phases compared to the mean total strength in the placebo-supplemented group. Wks. 1,9,10 with the increased volume saw a decrease in strength increases, especially for the placebo group.
A double-blind placebo-controlled trial into the impacts of HMB supplementation and exercise on free-living muscles protein synthesis, muscle mass and function, in older adults. (Din et al., 2018).	16 healthy older men, 8 placebo 68.5 +- 1.0 and 8 treatment 67.8 +- 1.1.	HMB (hydroxy-methyl-butyrate free acid) given as an oral 3g dose per day in 1g sachet form taken trice daily.	6wks intervention with a resistance exercise training program completed 3x per week for the duration of the intervention.	Unilateral leg (Vastus Lateralis) measured 1-RM (MVC measured with isometric contractions using an isokinetic dynamometer.	1-RM was determined for dominant leg. Leg extensions used for 6 sets of 8 reps at 75% 1-RM. 1-RM and MVC was assessed every 10-days.	1-RM was measured every 10-days for the first 4wks and at 6wks.	Over the 6-week period RET increased 1-RM linearly in the trained leg in both groups with increases after just 3wks. Evidencing that there was no difference with HMB. (MPS was shown to increase in the first 2-weeks).

Effect of calcium HMB (CaHMB) with and without resistance training in men and women 65+ yrs.: A randomized, double-blind pilot trial. (Stout et al., 2013).	Phase 1: 21 participants (male and female) for placebo group and 22 for HMB. Phase 2: 20 for resistance training and placebo and 16 with CaHMB and resistance training.	Phase 1 non-exercise group (a) Placebo and (b) 3g CaHMB consumed twice daily. Phase 2 same as before with the addition of resistance training for a and b. 3-day dietary recall pre-mid-post testing.	24wks duration with Phase 2 resistance training 3-days per week.	Isokinetic leg extensions. Peak torque (PT) during maximal voluntary concentric isokinetic leg extension and flexion muscle actions measured. Dynamic constant external resistance (DCER) strength testing was also used in Phase 2.	Phase 2 used a progressive RE program with 3 sessions a week for 21wks (excluding 3wks of testing). 80% of 1-RM used to perform 3 sets of 8-12 reps on the bench, lat pulldown, leg press, hack squat and leg extensions.	Test performed week 0 (pre-test), 12wks (mid-test) and 24ks (post-test)	Phase 1 results evidence no change in the PT for the placebo group. The HMB group increased mid and post-testing and significant at post-testing for leg extensor 60 degrees and 180 mid and post. Phase 2 Leg extensor 5RM significantly increased in both groups as did the testing for Isokinetic leg extensor PT. Evidencing that there was no sig between HMB and placebo with the addition of resistance training but there was an increase when used without.
Leucine-enriched protein supplementation dose not influence neuromuscular adaptations in response to a 6-month strength training program in older adults (Stragier et al., 2016)	There were 21 women and 14 older male participants. N10 male, n7 women (control); n12 male, n7 women (training + supplement) and n13 male, 7 women (training + placebo).	Three groups: 1- control n10; 7 women: 2- training and 20g protein enriched with leucine (supplement) n12; 7 women: Training and placebo n13; 7 women. However, 12 participants were randomly selected to measure time course muscular and neural adaptations, these data will be used for this analysis. Dietary assessment food survey over 7-days.	Duration of intervention is 24wks with strength training program twice weekly for duration.	Maximal voluntary contraction will be tested with the plantar flexor muscles of the right leg	Two 1-hour session per week. Leg press and calf raises used (3 sets of 10 reps initially). Incremental increases were used as a % of 10 RM and 5 sets of 10 (failure) repetitions used.	0 before, 12wks mid and 25wks end.	TP was used for MVC. No difference was observed in both groups, the statistical significance resulted from training. With a greater increase in MVC torque during the first 12wks than the second 12wks.A gain of 0.9% in the first 12wks, whereas the last 12wks only 0.25% gain. agreeing with (Panzer et al., 2015) (muscle size increasing post 12wks). Paper did not indicate that the intervention augmented muscle strength.

Protein supplementation before and after exercise does not further	Participants elderly men (n26; aged 72+-2 years)	10g of protein as casein hydrolysate before and after training therefore total of 20g. Standardised meals before test days, with 2-day diary pre-tests. 3-day diary before and at week 11.	Intervention 12wks resistance training program with protein or without (placebo)	Quadriceps. Strength measured by 1-RM test on leg-press and leg-extension machines.	12-week resistance training at 3 sessions per week. With 4-sets on both leg-press and extension for the first 4-weeks training increased from 60% 1RM (10-15 reps) to 75% (8-10 reps) then 75-85% with 8-reps week 5 onward increasing load according to new 1RM (being tested week 4 and 8)	0 start, 4wks, 8wks and 12wks (these data were not shown in the paper but were referred to in the results, only before and after were evidenced).	The results evidence that muscle strength increased before and after the intervention in both groups. However, the repeated-measures analysis showed increases in 1RM was statistically significant for each 4-wk intervention period for both exercises again with no difference between groups.
augment skeletal muscle hypertrophy after resistance training in elderly							
men (Verdijk et al., 2009)							
Effects of free leucine supplementation and resistance training on muscle strength and functional status in older adults: a randomized controlled trial. (Trabal et al., 2015).	30 participants, 15n placebo (84+-4 years) and 15n leucine (85+-8 years) initially. N12-completed 4wks in leucine group and n7 finished at week 12. N12 completed 4wks in placebo group and n4 completed 12wks.	10g leucine taken orally from the ingestion of 40g of protein twice per-day (40g equivalent to ≥ 4g leucine) with a total of 80g supplement each day. 3-day diary each time point.	12-week period of resistance training and supplement intervention.	Measurements were taken from maximal overcoming isometric leg strength. Performed on both legs at 130 ∘ leg flexion and measured with a dynamometer.	12 weeks of 3 resistance training sessions per week and 1 balance session adapted for older adults. 30-mins of strength training at 2-sets of 15-reps with an intensity of 65%. Lower extremities were prioritised. Chair squats, leg curls and extensions plus wall push-ups.	0 weeks, 4wks and 12wks. Although, only 7n completed the full 12wk inter-vention program and only 4 completed the placebo program.	Changes in strength reveal a beneficial effect in the leucine group over the placebo at both time points. The size effect was approx. 0.6 at both assessment points, interpretation of these data show leucine scores 73% high in adapation than the placebo group. However, there was no statistical significance at 12wks but between groups should be considered significant.

Protein Supplementation during Resistance-Type Exercise Training in the Elderly. (Leenders et al., 2012).	Participants included healthy elderly men (31n 70+- 1 yr.) and healthy elderly women (n29 70-+_ 1 yr.).	intervention group contained 12n men and 12n women and were given 15 g of protein (milk protein concentrate (MPC80). The milk protein consisted of 80% of casein and 20% of whey protein. Standardised meals pre-test days. Habitual eating encouraged. 4-day food diary.	24-week resistance training and supplement intervention.	Maximum strength was assessed by 1-RM test on leg-press and leg-extension machines. 1-RM tests were repeated after 4, 8, 12, 16, and 20 wk. of intervention and 2 d after the last training session of the intervention program.	Supervised resistance training program 3x wk. for a 24-week period. 4-sets on both leg press and extension three sets on the chest press and horizontal	1-RM tests were completed at 0, 12 and 24 of the intervention.	Baseline results indicated no initial difference but after 12wks there was an observed difference between placebo and protein groups (but not gender). Further increased were made between 12wks and 24wks. Leg extension increased 23% men and 22% women after 12wks, between 12-24wks increased by another 17 and 16% respectively. Supplementation does not augment an increase in strength adaptation.
					row; these four exercises were performed every training		
					session. The vertical lat pull and abdominals were alternated with biceps curl and triceps extension between subsequent training sessions. During the first 4 wk.		
					of training, the workload was increased from 60% of		
					1 RM (10–15 repetitions in each set) to 75% of 1 RM (8–10 repetitions). Starting at week 5, four sets of eight repetitions were performed at 75%–80% of 1 RM.		

The Effects of Low-Dose Creatine Supplementation Versus Creatine Loading in Collegiate Football Players. (Wilder et al., 2001).	25 (19+- 1.02 yrs.) highly trained male adults. Participants number for group 1 was n8, group 2 n8 and placebo n9.	Creatine supplementation in 3-groups, group 1 - 3gd for the duration of the study and group 2 - 20gd for 7-days followed by 5gd for the remainder of the study and a placebo group. Habitual diet, no supplements etc.	The study consisted of 10wks resistance training conducted for each group alongside the supplement intervention.	Legs. The 1-RM back-squat values were obtained before (week 0), during (week 5), and after supplementation (week 10).	Training program consisted of a periodized resistance regime during the intervention with 4h per week of heavy resistance and 4h per week of conditioning. The primary exercises in the strength program were	0 (start), 5wks and 10wks	Significant differences in absolute maximal strength were found over time with the periodized resistance training program (P 5 .001, F1,22 5 13.52); however, no group or interaction effects were noted (P 5 .232, F2,22 5 1.50) therefore, effects were significant regardless of supplement used, training being the predominant factor in adaptation. This study evidenced that creatine did not increase strength.
					the front squat, back squat, hang clean, power clean, overhead		
					press, bench press, single-arm dumbbell press, 1-arm rows, straight-leg dead lift, power shrugs, upright rows, chin-ups, dips, medicine ball plyometrics, and bumper-plate push-ups.		

Long-term creatine intake is beneficial to muscle performance during resistance training. (Vandenberghe et al., 1996).	19 healthy sedentary female adults (19-22 yr.). 2 groups creatine n10 and placebo n9).	In the first stage, the Cr group received 5 g of creatine monohydrate (2.5-g tablets) 4 times/day during 4 days (HD). This was followed by a period of 10 wk. during which the Cr group consumed 5g creatine monohydrate (2.5g 2 times/ day) (LD). Creatine and placebo tablets were identical in appearance and taste. Standardised meals pre testing.	Intervention was 10-weeks of 1h resistance training 3x per week with or without creatine supplementation.	Maximal muscle strength, 1 RM of leg press, bench press, leg curl, leg extension, squat, and shoulder press were determined before and after 5 and 10 wk. of resistance training in combination with creatine.	The training involved seven different exercises, including leg press, bench press, leg curl, leg extension, squat, shoulder press, and sit-ups. Each exercise consisted of 5 series of 12 repetitions at 70% of one repetition maximum (1 RM). The 1-RM values were determined before and again after 5 and 10 wk. of training.	0 weeks, 5 weeks and 10 weeks.	Placebo had sig increases in 3-exercise 1-RM at 5w compared to creatine group. All groups increased their 1-RM at week 10 with creatine showing a 20-25% greater increase in the squat. Indicating that creatine supplementation enhances strength after 5-weeks and increased sig against a placebo after 10-weeks thus adaption occurs as intermittent exercise capacity increases.

The nutritional interventions used in the selected studies include supplements containing protein including protein enriched with leucine, HMB and creatine. Of these studies ~64% utilised a self-reported food diary/log, the studies used dietary records of between 3 and 7-days to analyse habitual diets of the participants. Only ~9% of the studies utilised meal standardisation for the duration of their studies (25% protein, 50% carbohydrate and 25% fat) however, a further ~27% did require a standardised meal scheduled to be used the day prior to testing/measurements. It is interesting the note that ~55% of the studies reviewed focused on protein (including protein enriched with leucine) with ~67% of these studies using a minimum of 20g as an addition to habitual diet. HMB supplementation consisted of ~27% of the studies reviewed with a standardised 3g taken per-day. The remaining ~18% (n=2) studied the effects of creatine both these studies used a 'loading' phase of 20g per-day split throughout the day followed by a maintenance phase, using 5g per-day for one study. The second study had a high (5g) and low (3g) loading phased approach for 4-days (total of 20g and 12g respectively) then maintenance of 5g and 3g respectively for the remaining duration. Regarding resistance strength, analysis of upper and lower limb muscle groups were tested and measured with ~73% of test completed on the lower limbs and ~27% on both upper and lower body tests. The tests used to measure the strength of the muscle included 1-repetition maximal lift (1RM) and/or dynamic training strength (5RM) and/or isokinetic strength measurement or a mixture of all three. Of these measures 1RM was the most prevalent measure used (with ~73% of studies using this method) with ~36% of the studies using isokinetic strength measures either independently or with other measures (other measurements e.g., free-fat mass was taken in each study; however, these measures were not directly pertinent to this review albeit very interesting).

The results of the reviewed studies are consistent with previous studies relating to the adaptation of skeletal muscle to resistance type training with specific regard to this review where studies were categorised to utilise high-magnitude training protocols >65% 1RM intensity. All of the reviewed studies evidenced adaptation to training regardless of supplement intervention or placebo given. However, it was interesting to note that Stout et al., 2013 evidenced that when HMB was taken as a supplement over a 24-week period without resistance training there were still significant mid- and post-testing adaptations. Interestingly, when resistance training was applied congruent to the previously mentioned paradigm there were significant changes at mid- and post-testing also however, there was not a significant difference between HMB and the placebo. Which contradicts Wilson et al. (2013) which demonstrated that HMB supplementation was significantly greater at 4, 8, and 12-weeks than the control group. The results of the protein supplement intervention confirmed that resistance training with high-magnitude led to increases in muscle strength adaptation at each time-point. All of the studies utilising protein as the supplement intervention used a control to evidence contrasts with the exception of (Esmarck, et al. [30]) which used pre-exercise and 2-hours post-exercise supplement interventions as comparisons rather than using a non-training placebo, again these showed mid-point (6-weeks) and post-trial (12-week) significant results, yet with no differential between interventions. The other protein interventions reviewed indicate there was no significance between intervention and control group regarding strength increase measurements. With the exception of (Trabal, et al. [63,64]) which evidenced that although there was no statistical significance at 12-weeks for isometric leg strength gains, between-group differences could be considered clinically significant at each time-point.

Creatine supplementation has been universally accepted to enhance performance with multiple short-term work bouts, improve recovery and long-term adaptation to training (Vandenberghe, et al. [59,60,43,65,49]). This review contained two studies that used creatine supplementation based on the criteria of reviewing temporal dynamics of strength adaptation and the differential between creatine consumption in the short-term and a control. The results of the two studies included in the review are not concomitant with each other, the results differ as (Wilder, et al. [45]) evidence significant time effects for 1RM strength increases, before and during, and during and after, and before and after supplementation. However, these data are similar to the control group which also showed increases in maximal strength thus showing that the addition of creatine (both low and high does) did create a significant differential (noting that the participants were trained athletes and their diets were not standardised). However, (Vandenberghe, et al. [59]) evidenced that creatine supplementation significantly increased 1RM strength after 5-weeks of resistance training with all six-exercise measured test showing improvements by +25 to +57% whereas, the placebo only increased in three measures tested (+15 to +40%). At 10-weeks the creatine group again showed greater difference in all strength tests evidencing that in lower leg measurements there was a 20-25% greater strength adaptation than the placebo group. Thus, indicating that creatine supplementation can enhance strength over the short-term as well as the long-term.

Based on the information gathered from the review it is in congruent that the current strength training paradigm does evoke adaption of muscle tissue. However, it has also been established that a strategy of adequate nutrition in the form of additional protein potentiates the adaptation of muscle tissue as a result of resistance exercise (Cermak, et al. [3]). Moreover, of the studies reviewed that used protein as a supplement (with a control/placebo) ~80% evidenced no statistically significant differential between supplement intervention and placebo at each time-point. Overall, this review does evidence that there was an increase in strength adaptation at the mid-point of each study for both intervention group and placebo (a mean time-point of 6.7-weeks). Additionally, further adaptation at the end of each 10-week and 12-weeks with additional increases thereafter in the three studies lasting 24-weeks. In Summation, there are a plethora of variables that could impact and skew the results of this review, as the search criteria has concise constraints the quantity of studies included in the review limits the data. These results suggest the predominant factor in strength adaptation is resistance training at magnitudes >65% 1RM regardless of supplement intervention, age and gender.

Discussion

This review was designed to extrapolate evidence from relevant peer-reviewed papers related to the effect of supplements coupled with the mechanical modality of high-magnitude resistance training on the temporal dynamics of muscular strength adaptation. Presently, to the knowledge of the authors the present review is thought to be the first review conducted specifically focused on the effects of supplementation on the temporal dynamics of muscle strength adaptation. The results of this review are congruent to the paradigm that resistance training containing intensities of >65% of 1RM induces muscular adaptation resulting in the augmentation of strength (Hickson et al., [1,2,25,16]). At each time-point across the total population of the review there was an increase in strength adaptation for both the training with intervention groups and the 'control/placebo' groups (with training but no supplement intervention). Indicating that the main protagonist in muscle strength adaptation is resistance training. These data were expected, as previously cited via adaptation mechanisms initially as a result of neural drive and the adaptation thereafter (Schuenke, et al. [4]). The review evidence that the initial adaptation occurs at a mean of the studies reviewed of ~6.7-weeks, the 'mid' period of the studies reviewed. The was one study which was not within same parameters as the other studies, this study measured strength every 10-days for 40-days and then subsequently on the final day, day-60. Again, there were incremental increases but this time it was over a shorter period of time, with each 10-day period evidencing early onset adaptation which continued until the end of the study (worth noting that the participants were untrained healthy older men).

The trend of the control groups which involved resistance training with no supplement intervention corresponded to the results of the supplement intervention groups examined in the review. All the studies showed an augmented response to resistance training in muscular strength when a supplement was included to the participants habitual diet. Although, many studies included food-diaries to monitor nutritional intake to eliminate potential outliers, only one study actually requested standardised meals to be used by their participants throughout the trial (other studies used standardised meals prior to testing days). This lack of conformity within the selected studies could have had an impact on the supplement intervention groups. Moreover, the lack of diet control may have skewed the results of the supplement intervention group for the individual studies. As the nature of taking a supplement is an exogenous addition to a nutritional regime if the aforementioned diet has for example adequate protein intake, and the intervention group has an extra 20g protein per day this 'supplement' may not have such an impact as 40g per day. However, again noting that the results of the review for both the control and supplement intervention groups indicating augmented adaptation to resistance training regardless, with only ~27% showing significant difference between the two measures. These data are not indicative to current knowledge regarding supplementation particularly protein which has numerous purported benefits in muscular adaptation (Volek, et al. [23,28,7,32,39,63]). Moreover, with protein requirement post-resistance training being axiomatic there must be other considerations to contemplate within group difference i.e., the type of protein consumed, the amount of protein consumed, and the timing of the protein consumed (protein-feeding). It has been shown that the muscles response to amino acids (AA) is transient and that the amount of protein absorbed is limited, subsequent to a single bolus of whey protein, after a latent period of 45-minutes MPS was augmented by approx. 200% for up to 90-minutes post consumption. This was prior to normal absorption rates, regardless of the availability of intramuscular and/or plasma leucine and essential AA (Atherton, et al. [36,42,25]). Thus, evidencing that there is a response to saturation of AA for a limited time of between 60-90 minutes where the rates of MPS (which results in strength adaptation) augments before returning to normal levels regardless of the amount of protein consumed or the availability of protein at that time, this has been referred to as the 'muscle full theory' (Atherton, et al. [36]).

The 'muscle full theory' indicates that there is a finite level of protein that is required to elicit MPS, and that leucine is the prominent AA that triggers the response. However, it is interesting to note that only two studies used >40g of protein per-day. One study used a total of 48g of protein (40g whey and 8g casein) this was ingested within 2-hours of exercise and on non-training days in the morning with a habitual diet. Although, this study did evidence an increase in fat-free mass during the study and an increase in the strength parameters set over time it did not indicate significance between groups at each time-point (over a 10-week period). However, (Trabal, et al. [64]) evidenced that the use of 40g of protein (to achieve a minimum of 5g leucine content) taken twice per-day did show differences between groups which were considered clinically significant. The other studies appeared to use the standard paradigm for protein intake, with the accepted textbook standard being 20-25g of protein consumed post-exercise [15]. Notwithstanding, the amount of protein administered in the studies reviewed could have had an impact on the outcomes. Evidence from (MacNaughton et al. [17]) indicating that whole body resistance training responds more favourably to 40g of protein consumed post-training rather than the standard 20g of protein recommended post-resistance exercise. Although, this information seems contrary to one of the aforementioned studies in the review which administered >40g of protein (fat-free mass did increase which can be a marker for muscular adaptation), there is evidence that 40g of whey protein is the optimum amount of protein to consume to elicit maximum MPS (MacNaughton et al. [17]). Whereas the majority of the other studies in the review did not use the optimal amount of protein to elicit a response which may have led to limitations. Thus, utilising this methodology alongside Atherton's 'muscle full theory' would create a perfect post-exercise protocol to ensure participants could achieve maximal MPS therefore, ensuring the best possible conditions for muscle strength adaptation.

This review also highlighted the effects of HMB supplementation with ~27% of the papers reviewed administering HMB to their participants. With all of the studies using the standard dosing of 3g per day, this protocol has been shown to be the optimum dose to achieve the purported anticatabolic actions (Gallagher, et al. [50-53]). With HMB purporting to have anticatabolic actions as a result of acute bouts of resistance training where there is an increased breakdown of protein, HMB partly prevents this exercise induced proteolysis thus causing reduced muscle damage therefore, recovery becomes more expedient and gains in MPS follow. These effects have been observed in both young and elderly 70-plus adults (Nissen, et al. [55]). This is why HMB is being studied and why it may have benefits as a supplement for improving recovery and subsequent adaptation and muscular strength. Of the ~27% of studies administering HMB, ~33% of the studies reviewed evidenced significant difference between the control group and supplement intervention group. These data evidence that temporal dynamics is significant at each time-point however, the remaining ~67% of the studies evidence the contrary. Fascinatingly, the one study that used standardised meals ensuring that a minimum intake of 25% protein (thus perhaps changing the dynamics of their habitual diet) showed significant results in the difference between groups. Remarkably, one study (Stout, et al. [66]) showed that there was significance between a non-trained control group and a non-trained HMB supplement group, evidencing HMB can augment strength adaptations without resistance training.

The review also considered creatine as a supplement with ~18% of the studies reviewed using creatine as their supplement of choice. Understandingly, creatine was chosen as it is unquestionably one of the most researched supplements of the past 30-years, the efficacy of creatine is well documented; it augments phosphocreatine (PCr) energy stores; increasing PCr resynthesis; and reducing muscle damage through buffering the increases in lactate and hydrogen ions. However, there is no clear evidence that creatine directly enhances MPS and thus muscle strength adaptation however, it does impact performance positively by enabling greater force production. This creates an optimal environment to work/train with higher intensity over a short period of time, with this maximal intensity damage to the musculature is enhanced resulting in adaptation (Louis, et al.). Nevertheless, if you do not have rigorous training protocols with continued high-magnitude training but rather use low-magnitude training over a short period of time, there is little need for creatine as a supplement to buffer metabolites, or to implement direct MPS (Wilder, et al. [43-49]).

The two studies that applied creatine as their supplement intervention were not completely homogeneous, one study used highly trained individuals and the other study used sedentary adult females. They also used different loading and maintenance protocols with (Wilder, et al. [43]) using high and low doses (20g and 12g loading and 5g and 3g maintenance respectively) and (Vandenberghe, et al. [59]) using the standard 20g loading and 5g maintenance protocols. The results of the (Wilder, et al. [43]) study containing highly trained individuals evidenced an increase in both the control and intervention groups in strength adaptation. With hitherto, no within group significant differences at any time-point during the study for high or low dose regimes (the diets of the athletes were not standardised nor controlled also; the participants known supplement regimes may not have been adequately investigated). Whereas the results of (Vandenberghe, et al. [59]) containing sedentary participants evidenced significance at each time-point (5- and 10-weeks) between groups. These results indicate that creatine supplementation can impact muscle strength adaptation after only 5-weeks, whereas it is notionally accepted that repeated resistive exercises engaging the ATP-PC energy system evidences more expedient results than when 1RM measures are tested (Wilder, et al. [43]).

Notwithstanding, it would seem counterintuitive to use creatine as a standalone predominant supplement for strength adaptation as it is not a direct potentiate of MPS. Also, the level of intensity of the mechanical modulation needs to be high. To augment the adaptation of muscle tissue, protein and in particular the AA leucine and supplements derived from leucine i.e., HMB as previously noted would be the obvious supplement to administer in intervention protocol to increase muscle adaption [26]. Leucine functions directly with mammalian target of rapamycin (mTOR), during resistance training mTOR activation is inhibited by AMP Activated protein kinase (APMK) as AA become available for energy metabolism. However, during recovery AMPK activation is decreased and mTOR reaches peak activity and as mTOR is known as an important signalling molecule involved in muscle hypertrophy it is important to potentiate its activation [41,42]. To elucidate the relationship between mechanical loading and leucine, a group of young (24-years) and a group of elderly (63-66-years) participants received intravenously infused leucine post resistance-exercise and the results at the end of the 2-week trial evidenced that both groups increased their MPS (Yarasheski, et al. [67]).

This review does have its limitations, the number of peer-reviewed papers relating to temporal dynamics of strength training adaptations with a supplement intervention are inadequate. Of the studies reviewed there were few comparisons that could be met; with each having different dosages of the same/similar supplement, differences in supplement administered, age differences of participants, trained or untrained status, standardised meals or habitual diet etc. Nonetheless, there were enough similarities to draw trends, resistance high-magnitude training increased muscular strength adaptation regardless of age or activity levels, supplements provide additional adaptation in each study but only clinically significant in ~27% of studies reviewed. Most importantly temporal dynamics were evidenced, with changes in muscle strength adaptation at each time-point in each study. Notwithstanding, lessons can be learnt from the limitations of the review, with areas of improvement for future trials. Standardised nutritional meal plans must be adhered to alongside pre-intervention food-diaries to understand the habitual diets of all participants to ensure the gold-standard for nutritional interventions. This should be a fundamental requirement to ensure adequate data alongside the correct mechanical modulation techniques for muscular strength adaptations (dependant on age demographic and gender considerations) to standardise two clear elements.

It is interesting to reiterate that when standardised meals were incorporated in a study and also, when the supplement included >40g protein to be taken twice per day the results were positive at each time-point. This leads to the question that if strength adaptation in muscular tissue occurs earlier than expected (the majority of previous studies evidence before and after measures and are usually 8+ weeks in duration) how that impacts muscular synergistic tissues such as tendinous tissue. The discrepancy with temporal dynamics of muscle and tendon adaptation caused by the use of high-magnitude training could have implications on the mechanical loading of the complex, with the disparity between muscle strength and quality of the tendon stiffness to tolerate said mechanical loading. Again, this discrepancy could be exacerbated with the addition of nutritional supplementation.

As previously cited, supplementation of leucine post-exercise accelerates MPS and thus muscle tissue adaptation. However, there is also evidence in intervention studies that leucine also has an effect on collagen in tendinous tissue, with an augment in hydroxyproline content of the tension region, independently of training intervention and a greater increase in collagen synthesis when combined with exercise (Barbosa, et al. [68,69]). This would suggest that leucine has anabolic qualities for both muscular and tendinous tissue nonetheless, this adaptation may not be uniform. One might postulate that the impact of the supplementation intervention will exacerbate the increase in muscular strength without a corresponding increase in tendon stiffness. This may result in an imbalance within the muscle-tendon-unit, with the muscle producing more mechanical force this augmentation in mechanical demand on the tendon will lead to potential vicissitudes resulting in susceptibility to injury (Epro, et al. [70-93]).

Conclusion

This review suggests that muscular strength adaptation occurs as a result of high-magnitude strength training (>65% 1RM) regardless of age, gender and activity level after a short period of training with mean significant adaptations at ~6.7-weeks. These data correlate with both the training and placebo (control) groups in each trial and the supplement intervention groups with all groups experiencing augmented strength adaptation, and ~27% of the studies demonstrating significant differences between the placebo and the intervention groups. With the knowledge that initial adaptation of skeletal muscle when high-magnitude mechanical modalities are applied results in augmented muscular strength adaptation, the ingestion of supplements that could potentiate this effect to a greater extent need to be measured alongside tendinous tissue response. The potential differentiation in adaptation could create additional influence on the associated tendon tissue that may not respond as expediently as muscle tissue, resulting in potential tendinopathy. Moreover, an athletes' coach/trainer must be made aware of the potential counterintuitive nature of supplementation and that high-magnitude resistance training may elicit strength gains faster than expected as a result of exogenous nutritional support. Therefore, a nutritional framework alongside training regimes needs to be applied synergistically with repeated testing to ensure potential injury risk is limited. Furthermore, future studies need to look directly at the temporal dynamics of muscular and tendon tissue strength adaptation in relation to high-magnitude mechanical modulation with supplement intervention to explore potential discrepancies in time adaptation as to prevent vicissitudes.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2022.46.007312

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