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Molecular Basis and Practical Applications of Training, Nutrition and Recovery for Maximum Gains in Lean Muscle Mass: A Narrative Review for Optimizing Muscular Hypertrophy

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Context: Skeletal muscle hypertrophy is a key determinant of strength, athletic performance, and functional capacity across the lifespan, and is clinically relevant to sarcopenia and chronic disease. This review integrates molecular mechanisms (e.g., mechanotransduction and mTORC1 signaling) with practical training, nutrition, and recovery variables to support evidence-informed hypertrophy programming.

Evidence Acquisition: Literature was searched in PubMed, Scopus, ScienceDirect, and Google Scholar (January 2010 to March 2024) using Boolean combinations of terms related to hypertrophy, resistance training variables and techniques, protein/macronutrients, sleep, and recovery. Included evidence prioritized randomized controlled trials, systematic reviews/meta-analyses, and mechanistic studies relevant to training, nutrition, and recovery; case reports/editorials and endurance-only or unrelated populations/outcomes were excluded.

Study Design: Clinical narrative review.

Level of Evidence: Level 4.

Results: Hypertrophy is maximized when resistance training provides sufficient mechanical tension and effective fiber recruitment, with weekly volume as a central driver. Practical synthesis supports ~10 to 20 sets per muscle group per week, near-failure efforts (repetitions in reserve ~0-2), and distributing volume across multiple weekly sessions to maintain training quality and recovery. Nutritional support centers on adequate protein intake (≈1.6 g/kg/day; often 1.6-2.2 g/kg/day in trained athletes), with meal distribution (≈3-4 meals/day, ~0.4-0.5 g/kg/meal) as a practical strategy to sustain anabolic signaling. Energy availability and carbohydrate intake support training performance and glycogen-dependent workload (≈3-6 g/kg/day), and a moderate caloric surplus (~200-500 kcal/day) may aid lean mass gain while limiting excess adiposity. Recovery, particularly sleep, modulates hormonal homeostasis and protein metabolism; adequate sleep duration (7-9 h/night) is emphasized as foundational for adaptation.

Conclusion: An integrative approach to training, nutrition and rest offers the most actionable framework to maximize hypertrophy and strength while managing fatigue and individual recovery capacity.

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Strength-of-Recommendation Taxonomy (SORT):

- Training and Nutritional (SOR A/B): most recommendations are based on Level 1 evidence.
- Recovery and rest aspects (SOR B/C): Mechanistic evidence is high. More Level 1 evidence needed with hypertrophy-related outcomes.

Keywords: hypertrophy; muscle protein synthesis; exercise recovery; training; nutrition

Skeletal muscle hypertrophy (also known as "gains") is defined as an increase in muscle fiber size resulting from a positive balance between protein synthesis and degradation.[89] This adaptive process occurs in response to resistance training, where mechanotransduction converts mechanical stimuli into biochemical signals that promote muscle anabolism.[52] Hypertrophy is not only critical for sports performance and strength but also clinically important, as its impairment is linked to sarcopenia and various chronic diseases.[52]

Skeletal muscle is comprised primarily of 2 main types of muscle fibers—type I (slow-twitch) and type II (fast-twitch) fibers—that differ in their physiological characteristics and responses to hypertrophy training. Type I fibers are more fatigue-resistant, have higher mitochondrial density, and are optimized for endurance activities; they typically show slower and smaller hypertrophic responses to resistance training. In contrast, Type II fibers—particularly Types IIa and IIx—are more glycolytic and capable of generating greater force and power, and they exhibit a more pronounced hypertrophic response to resistance training stimuli, especially under high-load or explosive conditions.[7,47] Resistance training protocols that emphasize mechanical tension and recruit high-threshold motor units—such as those involving heavier loads or explosive contractions—tend to preferentially target Type II fibers, making them central to strength and hypertrophy development. Understanding these fiber-type-specific adaptations is essential for designing effective hypertrophy training programs tailored to a person's physiology and training goals.

ARE RESISTANCE TRAINING AND GROWING MUSCLE HEALTHY?

Health benefits of skeletal muscle hypertrophy (via resistance training) span multiple physiological systems. Regular resistance exercise increases muscle strength markedly, even in older adults or those with muscle weakness, which significantly improves functional capacity and aids recovery from injury (e.g., ligament rupture and hip fracture treatment) or neuromuscular conditions.[42,76,104] Enhanced muscular strength and size also bolster joint stability, decreasing injury risk; a meta-analysis showed strength training can reduce sports injuries by ~67%.[49] Such training benefits athletic performance, not only by boosting strength and power but also by improving muscular endurance and exercise efficiency.[85] Musculoskeletal adaptations include increased bone mineral density (notably in the hip and spine) that helps prevent osteoporosis,[59] and improved muscle quality (greater force output per unit muscle mass) in aging populations.[96] Resistance training favorably alters body composition, promoting fat loss and lean mass gains,[53] and induces metabolic improvements. These include a healthier blood lipid profile (significant decreases in total cholesterol, LDL, and triglycerides),[36] enhanced insulin sensitivity (lower homeostatic model assessment of insulin resistance and hemoglobin A1c levels),[51] and improved glucose tolerance and glycemic control,[10] which together reduce risk factors for cardiovascular disease. In addition, resistance exercise confers cardiovascular benefits such as modest reductions in resting blood pressure and increased aerobic capacity.[18] Resistance training also exerts anti-inflammatory effects; studies report significant decreases in chronic inflammation markers such as C-reactive protein with regular training.[15] Beyond these specific outcomes, resistance training contributes to healthy aging: it improves mobility and balance (thereby lowering fall risk) and has been linked to better cognitive function, improved cancer survivorship, and reduced all-cause mortality in the long term.[1]

WHAT FACTORS DRIVE GAINS?

At the molecular level, muscle growth is regulated primarily by the mechanistic target of rapamycin complex 1 (mTORC1) pathway—a key controller of protein synthesis. mTORC1 is activated by mechanical load, amino acids, and growth factors such as insulin-like growth factor 1 (IGF-1), which signals via the PI3K-Akt cascade to enhance mRNA translation and ribosomal biogenesis.[88] Notably, mechanical overload can also activate mTORC1 independently of IGF-1 through cytoskeletal deformation, integrin activation, and the production of phospholipids such as phosphatidic acid (PA), enabling hypertrophy without direct hormonal mediation.[89] Conversely, inhibitory signals such as myostatin (a transforming growth factor-β family cytokine) suppress hypertrophy by activating the Smad2/3 pathway, reducing protein synthesis, and upregulating catabolic gene expression. Inhibition of myostatin has been linked to enhanced hypertrophic capacity and is a target for strategies aimed at boosting muscle growth.[86,89] In addition to these molecular mechanisms, the proliferation and activation of satellite cells play an essential role in sustained hypertrophy. These muscle stem cells respond to mechanical overload by

fusing with existing fibers, thereby adding new nuclei that expand the muscle's biosynthetic capacity. The activation of satellite cells is regulated by transcription factors such as the master transcription factor for myogenic differentiation 1 (MyoD) and myogenin, which are crucial for muscle regeneration and hypertrophic adaptation.[67,89]

Resistance training variables, such as volume, intensity, frequency, proximity to mechanical failure as inability to perform another repetition with the same load in a reasonable form (repetitions in reserve [RIR]), and interset rests significantly influence hypertrophic outcomes. Current evidence suggests that performing 10 to 20 sets per muscle group weekly, with 1 to 2 minutes of rest between sets and an RIR of 0 to 2, optimizes muscle growth.[7] Although training to failure was once considered essential, recent studies indicate that maintaining an RIR of 2 to 4 can yield similar adaptations while minimizing excessive fatigue and enhancing recovery.[86]

Sleep and recovery are also critical for muscle growth. Sleep deprivation reduces mTORC1 activation and disrupts hormonal homeostasis, diminishing protein synthesis and favoring muscle catabolism. Recent findings show that poor sleep quality is associated directly with reduced muscle mass and increased adiposity, even among active people.[78,109]

Nutrition plays a crucial role in hypertrophy. Adequate protein intake is essential for postexercise protein synthesis. An intake of approximately 1.6 g of protein per kilogram of bodyweight per day optimizes hypertrophic responses in young adults, whereas older adults require at least 1.2 g/kg/day to overcome anabolic resistance. Distributing protein intake across 3 to 4 meals with at least 0.4 to 0.5 g/kg/meal maximizes mTORC1 stimulation and muscle protein synthesis (MPS).[71]

The goal of this narrative review is to give clear and concise guidelines for optimizing muscle hypertrophy considering cellular adaptations and molecular pathways from the viewpoints of training, recovery, and nutrition. All these areas will be expanded upon in their own sections, allowing for both practicing clinicians, trainers, and athletes of all levels, as well as other researchers in the area, to grasp the key factors required to optimize hypertrophy and muscular development.

METHODS

Literature Review Strategy

This narrative review was conducted to synthesize and integrate current scientific evidence on optimizing skeletal muscle hypertrophy through resistance training, nutrition, and recovery strategies. Given the broad scope of the topic and its translational relevance for both clinical and athletic settings, a narrative review format was chosen to allow for in-depth discussion and cross-sectional analysis of diverse study designs.

Search Strategy and Databases

The literature search was performed using PubMed, Scopus, ScienceDirect, and Google Scholar. Searches were conducted from January 2010 to March 2024, with a focus on the most recent and high-impact publications whenever possible. Relevant studies published before 2010 were included if they were considered seminal or frequently cited in the current literature. Keywords and search terms used in Boolean combinations (AND/OR) included "hypertrophy," "resistance training," "muscle protein synthesis," "mTOR," "mechanical tension," "metabolic stress," "muscle growth," "training volume," "training intensity," "proximity to failure," "repetitions in reserve," "RIR," "advanced resistance training techniques," "drop sets," "blood flow restriction," "rest-pause," "protein intake," "amino acid profile," "leucine," "muscle gain," "caloric surplus," "carbohydrates," "fats," "anabolic hormones," "recovery," "sleep," and "circadian rhythm."

Inclusion Criteria

Studies were selected based on their relevance to the 3 primary domains of hypertrophy optimization: (1) training variables (e.g., volume, intensity, frequency, rest intervals, failure proximity); (2) nutritional strategies (e.g., protein and amino acid intake, macronutrient balance, nutrient timing, dietary periodization), and (3) recovery mechanisms and modalities (e.g., sleep, circadian rhythms, hormonal regulation).

Types of Study Included

Randomized controlled trials; narrative reviews; systematic reviews; overviews; meta-analyses; mechanistic studies (especially those involving molecular pathways such as mTORC1, IGF-1, AMPK, and satellite cell activation); observational cohort studies when experimental data were scarce; seminal theoretical frameworks in periodization and training physiology were included.

Exclusion Criteria

Excluded from this review were: (1) case reports, editorials, and conference abstracts lacking peer review; (2) studies with unclear methodology or lacking data relevant to hypertrophy mechanisms; (3) trials focused solely on endurance training or unrelated clinical populations.

Selection and Synthesis

Preference was given to studies with high methodological quality, sufficient sample sizes, and relevance to practical applications in sports science, nutrition, and human physiology. Overviews and reviews of the specific topics (training, nutrition, or rest) and subtopics (molecular mechanisms, advanced techniques, specific macronutrients) were considered as a preferred starting point.

Findings were organized into thematic sections, each of them including the molecular mechanical aspects associated with muscle hypertrophy: (1) molecular mechanisms of hypertrophy; (2) training variables and advanced techniques; (3) nutritional determinants and macronutrient strategies; (4) recovery and sleep optimization. This strategic approach allowed the authors

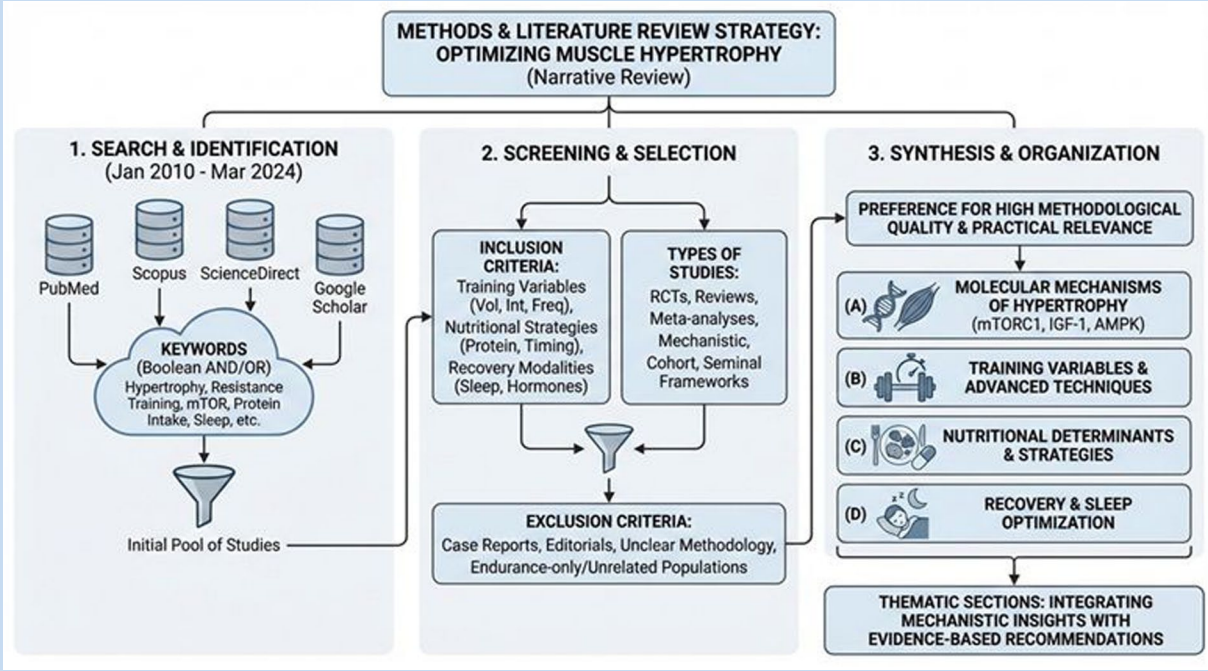


Figure 1. Summary of the narrative methodology of this research. Studies were selected based on methodological and practical relevance, guided by 3 main thematic sections: resistance training, nutrition, and recovery.

to integrate mechanistic insights with evidence-based recommendations applicable to athletes, trainers, clinicians, and researchers alike.

A summary of this narrative review methodology is provided in Figure 1.

RESULTS

Exercise: The Key to Muscle Hypertrophy Is Resistance Training

Mechanical loading in skeletal muscle triggers an anabolic cascade via mechanotransduction, where mechanosensitive structures such as costameres—integrin complexes linking the extracellular matrix to the sarcolemma—detect tension and activate intracellular signaling pathways.[52,113] For instance, mechanical contraction stimulates focal adhesion kinase and phospholipase Cγ1, promoting the production of PA—a lipid second messenger that activates Hippo pathway effectors, namely yes-associated protein and transcriptional-coactivator with PDZ-binding motif, thereby upregulating anabolic genes such as leucine transporters.[50] The increase in PA further contributes to the activation of mTORC1, which is essential for MPS; indeed, inhibiting PA production reduces mTORC1 phosphorylation after overload.[52] Elevated mechanical tension, achieved with high loads or contractions near failure, activates anabolic pathways such as ERK1/2 and mTOR directly, whereas metabolic stress induced by the accumulation of metabolites (e.g., lactate, inorganic phosphate, and H^+ ions) during high-repetition or blood flow-restricted exercises may indirectly contribute to hypertrophy through cellular swelling, transient increases in anabolic hormones, and satellite cell activation.[32,50] A meta-analysis has confirmed that training with light loads until failure, which emphasizes metabolic stress, produces similar muscle size increases as training with heavy loads emphasizing mechanical tension (provided that maximal fiber recruitment is achieved) suggesting that effective mechanical tension is indispensable for hypertrophy while metabolic stress serves as a secondary modulator.[32,50,113] Moreover, training volume, defined as weight × repetitions × sets (sometimes simplified as the number of weekly sets per muscle group) exhibits a dose-response relationship with muscle growth, with an optimal threshold around 10 to 20 sets per week; volumes beyond this may yield diminishing returns or even negative effects if recovery is compromised.[6,7]

Although our focus in this narrative review is on integrating the main pillars of hypertrophy into a cohesive narrative, we invite readers to consider other narrative models and training variables as well. This comparative reading will not only highlight points of agreement with the present work but also provide new perspectives that may improve the planning and personalization of their training.[4,17]

Aerobic Training and Muscle Hypertrophy

While resistance training is the primary stimulus for muscle hypertrophy, incorporating aerobic training can be beneficial for overall health, body composition, and training capacity.

However, concerns have been raised about the potential "interference effect" of concurrent aerobic and resistance training. Historically, it was believed that aerobic training might impair hypertrophy due to competing molecular pathways.[38] Nevertheless, a wealth of evidence suggests this interference effect is context-dependent. Some considerations about aerobic training are included in the following section.

Resistance Versus Aerobic Training Alone

Systematic reviews and meta-analyses confirm that resistance training is superior to aerobic training in promoting hypertrophy, particularly in type II muscle fibers. While aerobic training can lead to mild hypertrophy, particularly in untrained people or through high-intensity intervals, it does not match the fiber-specific growth or strength gains seen with resistance training.[32,38]

Concurrent Training (Aerobic + Resistance)

The premise that aerobic training blunts hypertrophy has been challenged. Studies show that, when programmed properly, concurrent training does not significantly hinder hypertrophic outcomes and can even enhance muscle growth in some contexts.[66] For example, combining aerobic and resistance training can increase quadriceps volume more than resistance training alone under specific protocols.[57]

Training Variables Matter

The effects of aerobic training on hypertrophy depend on several factors such as intensity, frequency, volume, and modality. High-intensity or interval-style aerobic training (e.g., >80% HRR) appears to be more compatible with hypertrophy than long-duration, low-intensity aerobic exercise. Furthermore, performing aerobic and resistance training in separate sessions or at least 6 hours apart may reduce interference and allow for full anabolic signaling from resistance work.[56,66]

Practical Recommendations

Including aerobic training in a hypertrophy program can support recovery, cardiovascular health, and fat loss without impairing muscle growth—if carefully programmed. To minimize interference, practitioners are advised to:

- choose moderate- to high-intensity aerobic modalities such as cycling or rowing;
- limit aerobic training to 2 to 3 times per week if hypertrophy is the main goal;
- schedule aerobic and resistance training on separate days or sessions;
- avoid excessive aerobic training volume, especially endurance-style long-distance running.[77,95]

Training Volume, Intensity/Load and Frequency

Training volume (defined as the total work done in a session or over a week [usually measured as sets per muscle group]) is a key determinant of muscle hypertrophy. Dose-response relationships exist between training volume and muscle growth, although adaptations diminish when volume exceeds certain physiological thresholds.[6] Research indicates that a weekly volume of 10 to 20 sets per muscle group is generally sufficient for optimal hypertrophic adaptations in trained practitioners, while higher volumes may not yield extra benefits and could even impair recovery and long-term performance.[90,121]

Regarding set and repetition schemes, training with 6 to 12 repetitions per set at 65% to 85% of 1-repetition maximum (RM) (1RM) is considered optimal for inducing hypertrophy in most subjects (especially newcomers), while advanced lifters may need specific periodization.[32,33] Lighter loads (~30% to 50% 1RM) can achieve similar adaptations if taken to muscular failure, although they require more repetitions to generate sufficient mechanical tension.[20] At the same time, it has been shown that, while strength can be gained equally through a wide range of repetitions in reserve (RIR before failure), muscle hypertrophy is maximized when reaching failure or near proximity to it (RIR 1-2).[84] In addition, in advanced trainees, alternating between high and moderate loads and volumes in different sessions (a strategy known as periodization) may optimize hypertrophy and strength by leveraging both mechanical tension and metabolic stress.[6])Nevertheless, the positive effects of periodization schemes (especially undulating periodization) seem to be notable only in experienced trainees.[61] A detailed section on periodization is available below.

The dose-response relationship as a concept has been studied extensively in the context of resistance training interventions, particularly in hypertrophy. Literature suggests that increasing volume enhances hypertrophy up to a point, but excessive work (over 20-25 sets per week) may lead to cumulative fatigue, hinder recovery, and reduce subsequent training performance. In well-trained people, very high volumes might disrupt the anabolic-catabolic balance over time. For novice lifters, any range from low to high volume training induces significant strength gains, while for experienced trainees medium to high volume should be preferred for gains.[80] Recently conducted randomized studies show a strong preference for hypertrophy adaptations on muscles from the same subject (experienced lifters) when training with high volumes rather than with high loads.[111] Available evidence tends to point to novice lifters and experienced trainees as 2 different groups, with neuromuscular adaptations in both strength and hypertrophy occurring "easily" in new trainees on any repetition range. The case for experienced lifters is different, where low-volume/high-load training is highly preferred for strength (example for a single exercise: 5 sets of 5 repetitions at 85% RM) and high-volume/medium-load for hypertrophy (example for a single exercise: 10 sets of 10-20 repetitions at 60% 1RM).[34,35,111] In the context of the latter examples, it would be reasonable to assume a total of 10 sets per muscle group per week for strength and 20 sets per muscle group per week for hypertrophy.

Rest intervals between sets play a critical role in modulating physiological and molecular responses to resistance training, influencing hypertrophic outcomes directly. Short rest intervals

(30-60 seconds) are typically associated with higher metabolic stress and elevated hormonal responses, which can promote hypertrophy particularly in high-volume, low-load training schemes.[93] Conversely, longer rest periods (2-3 minutes) are more conducive to performance maintenance, greater total volume lifted, and higher mechanical tension, making them better suited for low-volume, high-load training aimed at maximizing muscle fiber recruitment and strength gains.[7] On a molecular level, short rest intervals may elevate anabolic signaling pathways such as mTOR and AMPK transiently due to accumulated fatigue, while longer rest supports sustained performance and greater MPS over time.[4] Therefore, rest duration should be adjusted strategically according to the training goal: shorter rests can be used to amplify metabolic stress in hypertrophy volume-based sessions, while longer rests are suitable to maintain intensity and mechanical load in strength-oriented training.

Training frequency (how often a muscle group is worked per week), also plays a role. Although total volume is the primary driver of hypertrophy, distributing the same volume over 2 to 3 sessions per week (rather than 1) can enhance training quality and recovery.[6,121] In the case of elderly trainees, >2 training days per muscle group per week appear to offer no significant benefits on hypertrophy or strength.[44] An example application for trained lifters would be to train each muscle group twice a week, with 48 to 72 hours of rest in between sessions involving the same muscle group.

Maximum recoverable volume (MRV) is defined as the highest training volume a person can tolerate while still fully recovering and making adaptive progress, particularly in muscle hypertrophy. Operating near MRV is thought to optimize muscle growth by maximizing training stimulus without leading to nonfunctional overreaching or overtraining syndrome.[91] Training volume is a key driver of hypertrophy, with evidence supporting a dose-response relationship up to a certain threshold, beyond which recovery may be compromised.[7] Individual MRV is influenced by factors such as training status, sleep quality, nutrition, and stress levels, meaning it must be autoregulated rather than fixed. Effective application of MRV involves gradually increasing weekly training volume over mesocycles, monitoring recovery markers (e.g., soreness, fatigue, performance), and implementing periodic deloads to dissipate accumulated fatigue (more on these ideas in the periodization section).[4,29] Structuring training to remain just below or at MRV allows for maximum stimulus without exceeding the body's recovery capacity, making it a valuable concept in hypertrophy-focused resistance training programming. It is important to note that disease states (autoimmune, chronic inflammatory conditions, cancers, etc) also affect MRV; consideration should be given to this when tailoring training protocols.[13,55]

Proximity to failure, measured as a low number of repetitions in reserve (RIR 0-2), is key to maximizing the recruitment of high-threshold motor units. This approach increases mechanical tension and activates anabolic pathways, notably mTOR, which is essential for MPS. While training close to failure is critical for hypertrophy, consistently training to absolute failure may lead to excessive fatigue and impaired recovery, so maintaining an RIR of 0 to 2 is recommended to optimize muscle growth without compromising overall performance. At the same time, it has been seen that training each set at RIR 1 to 2 induces at least the same hypertrophy effects as total failure.[82,114]

Time under tension (TUT)—the duration of muscles being actively engaged during each repetition—also influences the hypertrophic response by modulating both mechanical tension and metabolic stress. Studies comparing slow (6 seconds per phase) with fast (1 second per phase) repetitions found that a longer TUT significantly increases mTOR activation and MPS in the 24 hours after exercise.[11] However, over the long term, a moderate repetition duration (0.5 to 8 seconds) does not significantly affect hypertrophy if training is taken to failure; only extremely slow tempos (>10 seconds per repetition) may be suboptimal as they reduce the total load lifted and the number of repetitions possible.[94] In practice, simply standardizing concentric and eccentric tempo for each exercise could help assess volume more effectively.

Advanced Resistance Training Intensification Techniques

Advanced resistance training techniques (RTTs) aim to intensify mechanical tension, metabolic stress, and muscle damage—key drivers of hypertrophy. When traditional protocols plateau in effectiveness, these methods offer a novel stimulus to enhance muscle growth. Recent research has explored several advanced techniques, highlighting their mechanisms and efficacy. While no particular order of "effectiveness" has been laid out clearly in the literature, we have ordered these techniques in descending order, depending on their perceived level of evidence and potential for improving hypertrophic outcomes (we therefore credit drop sets and blood flow restriction [BFR] the most). These methods are best suited for experienced trainees rather than newcomers.[2]

Drop Sets. Drop sets involve performing an exercise to failure, then reducing the weight (between 20% and 50% could be a reasonable range) and continuing without rest until new failure is achieved. Subsequent drop sets can be stacked on top of each other, but this can increase fatigue dramatically. This technique enhances metabolic stress and training volume in a time-efficient manner. Studies suggest that drop sets can be more effective than traditional sets for hypertrophy due to prolonged muscle activation.[43,47] Evidence even suggest that superior muscular gains in hypertrophy can be achieved with a single drop set compared with 3 sets of traditional resistance training at 12 maximum repetitions.[28] Some researchers recommend performing drop sets on machines, as they allow for better stability and significantly reduce injury potential in such a highly fatiguing scenario.[103]

BFR Training. BFR involves low-load training (~20% to 30% 1RM) combined with partial venous occlusion, which creates a hypoxic and metabolically stressful environment.

This approach increases significantly the phosphorylation of key mTORC1 proteins (e.g., p70S6K/S6K1, ribosomal S6) and elevates MPS—effects observed even in older adults, with a 56% postexercise protein synthesis increase at 20% 1RM.[22,30,69] In addition, BFR elevates anabolic hormones such as growth hormone due to metabolite accumulation and enhances satellite cell activation, collectively mimicking the hypertrophic stimulus of high-load training.[7,39,47]

In practice, BFR hypertrophy work is usually implemented by placing a pneumatic cuff or elastic band proximally on the limb, inflating to an individualized pressure of around 40% to 80% of limb occlusion pressure, and performing low-load resistance exercise at ~20% to ~30% 1RM for 3 to 4 sets with short interset rests (typically 30-60 seconds), often using a 30-15-15-15 repetition scheme while maintaining cuff inflation throughout the set cluster. Position-stand and guideline papers recommend applying BFR 2 to 3 times per week for 6 to 12 weeks, prioritizing multi-joint lower- or upper-body exercises and closely monitoring perceptual responses (rate of perceived exertion, pain) and any unusual symptoms.[75] Randomized trials and meta-analyses indicate that, when these parameters are followed, low-load BFR produces muscle hypertrophy comparable with traditional high-load resistance training and superior gains to low-load training without BFR in both young and older adults, while maintaining an acceptable safety profile when individualized pressures and appropriate supervision are used.[79]

Rest-Pause Training. The rest-pause training (Myo-Reps) method uses short rest intervals (e.g., 20 seconds) in a set to allow brief recovery and continuation of work. It enables high training intensity with elevated motor unit recruitment, possibly enhancing hypertrophy outcomes.[43]

In practice, rest-pause training involves an initial near-failure set (60% to 80% 1RM), followed by very brief pauses (10-20 seconds) and mini-sets (2-4 repetitions) to a target volume. Research shows it sustains high neuromuscular activity, achieves equal or greater volume in less time than traditional sets, and yields comparable or slightly superior strength and hypertrophy gains over 6 to 12 weeks. It is therefore a time-efficient method that effectively preserves motor-unit recruitment and hypertrophic stimulus.[26]

Accentuated Eccentric Loading. The accentuated eccentric loading (AEL) technique emphasizes the eccentric (lowering) phase of an exercise, using greater loads than in the concentric phase. It increases mechanical tension and may stimulate greater hypertrophic adaptations, particularly in well-trained people.[47] While potentially helpful, evidence of its effectiveness is not conclusive and as it works with a load higher than that concentrically manageable, could potentially lead to higher muscle soreness and injury rates if not properly assisted.[4,47,115]

AEL is a specialized training method for intermediate-to-advanced lifters, best applied to large, multijoint exercises (e.g., squat, bench press) with safety equipment. Protocols typically use 3 to 4 sets of 4 to 10 repetitions, 1 to 2 times weekly for 4 to 10 weeks, with the eccentric load set 20% to 40% higher than the concentric load. Eccentric overload requires specialized equipment (e.g., weight releasers, flywheels) and involves a controlled eccentric contraction (~2-4 seconds) followed by an explosive concentric. Total weekly volume should be maintained by reducing other work. Research indicates AEL offers only modest hypertrophy benefits over traditional training (~10% vs ~7% growth) and is best used as a short-term intensification block for strength and high-tension exposure, not as a primary year-round method. Due to higher forces, muscle damage, and soreness, careful progression is essential. Implementation requires a traditional training base, familiarization sessions, strict supervision, and safety measures. We recommend starting conservatively (e.g., 100% 1RM eccentric contraction, 70% to 80% 1RM concentric contraction) with low weekly exposure, adjusting based on soreness, pain, or technique.[9,116]

Cluster Sets. Cluster sets incorporate brief rest intervals between repetitions, enabling maintenance of higher loads and power output over a set. This preserves mechanical tension and training quality, which are both conducive to hypertrophy.[47]

In practice, cluster sets involve breaking a set into small groups of 1 to 3 repetitions at high loads (70% to 90% 1RM), separated by brief intraset rests (~10-30 seconds). This configuration maintains higher bar velocity, power output, and repetition quality compared with traditional straight sets, thereby better preserving mechanical tension per repetition. While long-term studies show cluster and traditional sets yield comparable strength and hypertrophy gains when volume and effort are equated, cluster sets induce less neuromuscular fatigue and smaller performance decrements. Practically, they are best applied to compound lifts (e.g., squats, presses) to maintain technique and bar speed or used in phases emphasizing high-tension repetitions without excessive fatigue. Within periodization, clusters can be implemented as short blocks or for quality emphasis, provided weekly volume and proximity to failure align with recoverable capacity.[19,110]

Supersets and Agonist-Antagonist Pairings. Supersets, particularly upper-lower body or agonist-antagonist pairings, increase training density and can lead to greater metabolic stress. These strategies are time-efficient and may enhance the overall training stimulus.[47]

Supersets pair 2 exercises performed consecutively with minimal rest (0-30 seconds), followed by a longer rest interval (~60-120 seconds). In hypertrophy training, agonist-antagonist pairings (e.g., bench press + row) or upper-lower body pairings (e.g., squat + bench press) are performed with moderate loads (60% to 80% 1RM) for 8 to 15 repetitions over 3 to 4 supersets. This configuration increases training density, reduces session time by 30% to 40%, and maintains comparable volume and long-term adaptations in strength and hypertrophy. Acute benefits include preserved bar velocity, repetition performance,

and potential volume load increases. Agonist-antagonist pairing facilitates interset recovery of the opposing muscle group and can be modulated for lower fatigue or higher metabolic stress. Practically, supersets are suitable for accessory exercises or phases prioritizing time efficiency and metabolic stress, provided total weekly volume and proximity to failure align with the athlete's recoverable capacity within the periodized plan.[12]

Sarcoplasmic Stimulating Training. Sarcoplasmic stimulating training (SST) focuses on increasing sarcoplasmic volume through high-repetition/high-volume/low-load training, targeting the noncontractile components of muscle size. It is proposed to contribute to size increases distinct from myofibrillar hypertrophy.[47] To manage fatigue and damage effectively, SST should be used sparingly in a periodized program, ideally during phases focused on metabolic conditioning or as a novel stimulus when traditional training has plateaued.[43]

SST is an advanced resistance training method that uses light loads (30% to 60% 1RM), high repetitions (12-25+), and very short rest intervals (30-60 seconds) to maximize metabolic stress and cell swelling as a hypertrophic stimulus. This method is typically implemented for 1 to 2 exercises per muscle group in a session, programmed at the end of a workout after heavier work or within dedicated 3- to 6-week mesocycles to elevate volume without increasing mechanical load. The physiological rationale is that low-load training to failure can produce hypertrophy comparable with heavier loads, mediated by metabolite accumulation (lactate, inorganic phosphate, H^+) and the resultant cell swelling and hypoxia, which potentiate anabolic signaling. Practically, coaches implement SST using loads of 30% to 50% 1RM for 3 to 5 sets of 15 to 25 repetitions taken to near failure, with 30 to 60 seconds rest and an emphasis on continuous time under tension through controlled tempos and limited lockout pauses. This training is best used sparingly as a supplemental hypertrophy block within a broader periodized plan, not as a year-round primary methodology.

Manipulating Repetition Tempo and Range of Motion. Moderate tempos (2-8 seconds per repetition) and emphasizing lengthened muscle positions enhance hypertrophic response. Very slow repetitions (>10 seconds) are less time-effective as they do not significantly increase hypertrophy.[4,7,94]

In practical terms, hypertrophy-oriented programming is best served by moderate repetition tempos and an emphasis on training in lengthened positions, rather than extremely slow lifting. Meta-analytic work indicates that when sets are performed close to failure, a wide range of repetition durations from ~0.5 to 8 seconds per repetition produces similar muscle growth, so a pragmatic prescription of roughly 2 to 8 seconds per repetition (e.g., ~1-2 seconds concentric and ~2-4 seconds eccentric) allows lifters to control the load without sacrificing volume or intensity. In contrast, both an umbrella review and related systematic work report that very slow repetitions (≥10 seconds per repetition) tend to yield inferior hypertrophy and much lower training efficiency, since the same set duration limits the total load and number of stimulating repetitions that can be accumulated. With respect to range of motion (ROM), recent randomized trials and systematic reviews show that training at longer muscle lengths—either via full ROM or lengthened partials (e.g., deep squats, incline curls, overhead triceps work)—often produces equal or greater hypertrophy, particularly in distal regions of the muscle, compared with work biased toward shorter muscle lengths. Accordingly, coaches can cue lifters to use a controlled but not excessively slow tempo within this moderate window, while prioritizing exercises and joint angles that place the target muscle under tension in its stretched position, which together appear to maximize the hypertrophic return for the time invested.[7,94]

Periodization

Periodization refers to the systematic manipulation of training variables such as volume, intensity, frequency, and rest, to optimize performance and adaptation over time. In the context of hypertrophy, periodized training plans aim to balance mechanical tension and metabolic stress by alternating between high-volume, low-load and low-volume, high-load phases. This approach enhances muscle growth while managing fatigue and reducing the risk of stagnation. The available evidence suggests that when equating for volume between conditions, periodized resistance training protocols have a greater effect on strength (measured as 1RM) compared with nonperiodized protocols.[61]

Periodization allows for progressive overload while minimizing the risk of overtraining—a critical factor in sustained hypertrophic adaptation. Research shows that nonperiodized programs may lead to plateaus, whereas structured periodization enables continued adaptation through novel stimuli. By manipulating volume and intensity, the neuromuscular system is continually challenged, promoting both sarcoplasmic and myofibrillar hypertrophy.[7]

In resistance training periodization, several key structural units guide program design: the macrocycle, mesocycle, and microcycle. The macrocycle typically refers to the overall long-term training plan, often spanning several months to a year. This is divided into mesocycles, which are medium-length blocks (usually 3-6 weeks) focusing on specific training goals such as hypertrophy, strength, or recovery. Each mesocycle is further divided into microcycles, which are shorter intervals (typically 1 week) where daily and weekly training variables are manipulated to achieve the objective of the mesocycle.[7] This hierarchical structure allows for precise progression, recovery planning, and fatigue management, which are essential for long-term hypertrophic gains and program adherence.[29,54]

- High-Volume, Low-Load Training Phases: high-volume, low-load training (e.g., 12-20 repetitions per set, shorter rest periods) emphasizes metabolic stress and increased time under tension. This method increases sarcoplasmic hypertrophy and may enhance muscle glycogen storage and cell swelling, contributing to muscle size gains.[47] Incorporating this approach into a mesocycle improves

training density and can be especially effective when combined with techniques like drop sets or BFR to further intensify the metabolic load.[4]

- Low-Volume, High-Load Training Phases: in contrast, low-volume, high-load training (e.g., 4-8 repetitions per set, longer rest intervals) promotes mechanical tension, which is a key driver of myofibrillar hypertrophy. This training strategy recruits higher-threshold motor units, making it especially effective for developing strength alongside hypertrophy.[91] Periodizing such phases into a hypertrophy-focused program ensures maximal muscle fiber recruitment while allowing the nervous system to adapt to heavier loads.
- Deload weeks: these are planned periods of reduced training volume and/or intensity designed to mitigate accumulated fatigue, promote recovery, and enhance long-term progression. While direct research on deloading is limited, evidence from periodization literature supports its use for preventing overtraining and preserving performance during prolonged hypertrophy phases.[29] Deloads are particularly beneficial after high-volume mesocycles or when signs of overreaching—such as persistent soreness, sleep disruption, or reductions in performance—begin to appear.[4] Effective deloading typically involves reducing volume by 30% to 50%, maintaining or slightly lowering intensity, and preserving movement patterns to prevent detraining. Strategically inserting deload weeks every 4 to 6 weeks can help sustain training momentum and maximize hypertrophic adaptations over the long term. There is no significant evidence supporting prolonged full time off from training.[107]
- Undulating and Block Periodization Models: undulating periodization alternates training variables within a week or microcycle, such as switching between high-volume and high-intensity sessions. This method maintains training novelty and stimulates both hypertrophic pathways concurrently. Block periodization, on the other hand, sequences distinct mesocycles dedicated to specific goals (e.g., accumulation → intensification → deload). Evidence supports the effectiveness of both models for promoting hypertrophy when properly integrated.[29,43] Reverse periodization in resistance training inverts the traditional model by starting a training cycle with higher intensity and lower volume, then shifting progressively toward lower intensity and higher volume. While a viable organizational framework, current evidence indicates it is not superior to other periodization models. A 12-week randomized trial found that while both linear and reverse linear models improved strength and body composition in resistance-trained women, the traditional linear approach produced larger maximal strength and hypertrophy gains when volume was matched. More broadly, systematic reviews conclude that reverse, traditional, and block periodization are all effective and largely equivalent for improving strength and muscular endurance, with no consistent evidence favoring the reverse model. Therefore, the utility of reverse periodization lies primarily in offering a different organizational logic that may prioritize high intensity early in a cycle, while overall training adaptations depend more critically on total volume, proper progression, and athlete adherence than on the specific direction of the linear progression.[31]
- Prolonged Time Off: there is strong evidence that prolonged time off from training (detraining)—especially beyond 1 to 2 weeks—can negatively impact both hypertrophy and strength, particularly in trained participants. A systematic review found that muscle strength gains from resistance training can be partially retained up to 16 to 24 weeks of detraining, but beyond that (e.g., 32-48 weeks), strength levels often return close to baseline, and there is insufficient data to draw firm conclusions about hypertrophy, although reductions are likely.[25] Another study demonstrated that, after just 3 months of detraining, previously gained muscle cross-sectional area and strength were reduced significantly, indicating both neuromuscular and structural regressions.[3] Interestingly, high responders to hypertrophic training tend to lose more muscle mass and strength during detraining than low responders, suggesting greater vulnerability to inactivity among those who initially gain more.[81] The decline in muscular strength after resistance training cessation is not uniform; it is more pronounced in older adults and inactive people compared with recreational athletes, with the magnitude of loss influenced by a person's training status, age, and the duration of the break.[8] In older adults, detraining for 12 weeks after resistance training led to significant declines in both muscle strength and muscle cross-sectional area, even though some gains were retained above pretraining levels.[107] Considering all this, we recommend that, if training absence is necessary, this time should not exceed 1 week off training to preserve obtained gains.

A summary of all the key points associated with resistance training modalities and variables for optimizing hypertrophy can be found in Figure 2.

Nutrition: Macronutrients and Strategies

Nutrition plays an essential role in optimizing muscle hypertrophy by fueling training, supporting recovery, and directly influencing MPS.[70] While resistance training provides the primary stimulus for muscle growth, it is the nutritional environment—especially protein and energy availability—that determines the extent of the anabolic response.[47] Protein intake remains the most extensively studied nutritional factor, with research consistently supporting that sufficient protein (both in quantity and quality) enhances MPS and facilitates lean mass gains when combined with resistance training.[73] In addition, energy balance, particularly maintaining a slight caloric surplus, is crucial for maximizing hypertrophy, as energy deficits can impair anabolic signaling and muscle recovery.[83,100] Beyond macronutrients, emerging evidence highlights the potential supportive roles of supplements like creatine, omega-3 fatty acids, and others.[73] This section will explore the critical

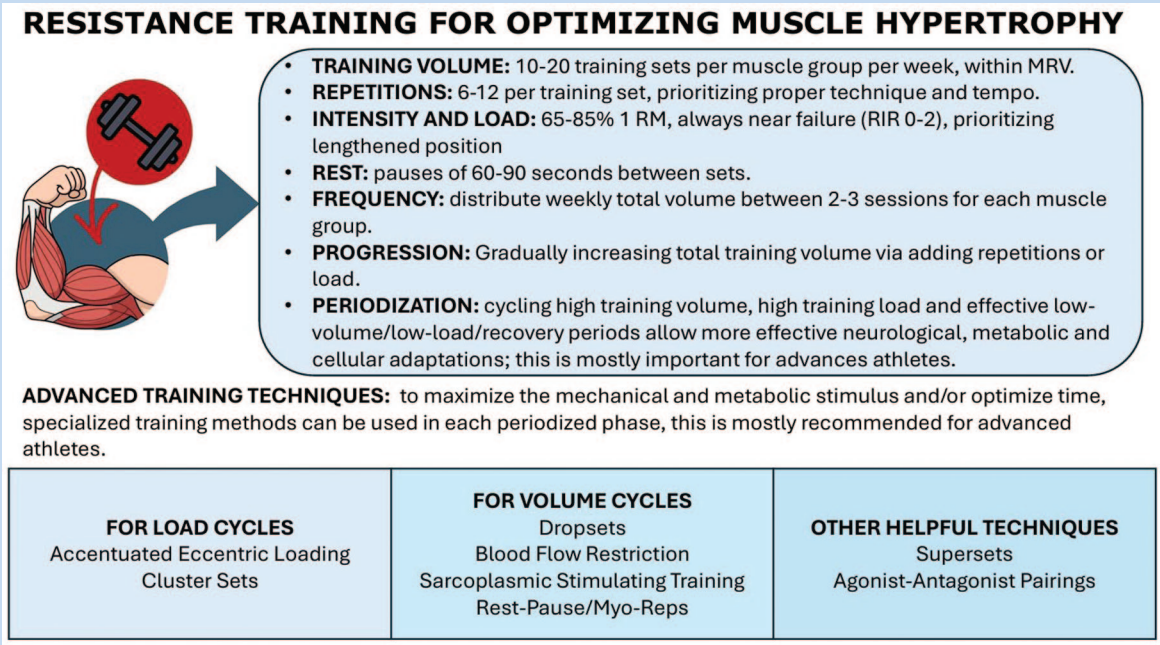


Figure 2. Summary of resistance training modalities and variables necessary for optimizing muscle hypertrophy, with mechanical tension and metabolic stress being the main drivers of MPS. In this context, training volume emerges across literature as the main training variable to tune up for maximizing muscle growth (considering same ROM and proximity to failure). 1RM, 1 repetition maximum; MPS, muscle protein synthesis; MRV, maximum recoverable volume; RIR, repetitions in reverse; ROM, range of motion.

nutritional strategies that enhance resistance training outcomes, including macronutrient intake (protein, carbohydrates and fats), energy availability, nutrient timing, and supplementation.

Energy Balance and Caloric Surplus

Energy balance is the primary regulator of muscle hypertrophy; however, an uncontrolled caloric surplus can lead to undesirable increases in adipose tissue. To maximize protein synthesis without excessive fat gain, a moderate caloric surplus of approximately 200 to 500 kcal/day is recommended as an addition to the total daily energy expenditure.[72] This surplus is sufficient to stimulate anabolism without causing excessive lipid storage.[100] Also, it has been seen that a caloric deficit of >500 kcal/day can effectively impair hypertrophy.[68]

Macronutrient Distribution

Adjusting macronutrient quality, amount and proportions is fundamental for optimizing muscle gains. An optimal distribution (around 50% carbohydrates, 30% fats, and 20% proteins) has been shown to favor muscle mass increases while preserving insulin sensitivity.[58]

Dietary Periodization and Protein Timing

Diet periodization, which involves alternating phases of caloric surplus with periods of maintenance or controlled deficit, has proven effective for improving the muscle-to-fat ratio.[64]

Proteins and Amino Acids

How Do Proteins Work for Muscle Growth?. Skeletal muscle growth is regulated by the interplay between mechanical and nutritional stimuli. Amino acid availability is critical for activating key anabolic pathways, such as mTORC1, and for inhibiting catabolic processes mediated by myostatin.[23] Adequate protein intake, along with proper distribution throughout the day, significantly enhances the hypertrophic adaptations to resistance training by promoting a net positive MPS.[65] The protein metabolism pathway is mediated by mTORC1, which integrates signals from nutrient availability, mechanical load, and growth factors like IGF-1. Activation of mTORC1 stimulates phosphorylation of p70S6K, enhancing muscle protein translation and ribosomal biogenesis.[92] In contrast, inadequate protein intake reduces mTORC1 activation and increases AMPK signaling, leading to protein degradation through the activation of ubiquitin ligases atrogin-1 and MuRF-1.[106] Note that the current evidence strongly suggests that isolated amino acids are not warranted to produce the same anabolic effects as whole proteins.[60]

What Does a Good Protein Source Look Like?

A high-quality protein for muscle growth should be evaluated based on its amino acid composition, particularly its content of essential amino acids (EAAs) and branched-chain amino acids (BCAAs), as well as its digestibility and absorption kinetics.

BCAAs (leucine, isoleucine, and valine) are especially critical, with leucine playing a central role in initiating MPS via activation of the mTOR signaling pathway.[119] Isoleucine and valine contribute by supporting energy production and recovery during training. A complete amino acid profile that includes all 9 EAAs is essential for sustaining MPS, particularly during prolonged or intense resistance training.[73] Digestibility and absorption speed are also critical; rapidly absorbed proteins such as whey have been shown to stimulate a robust, short-term increase in MPS, while slower-digesting proteins such as casein provide a more sustained amino acid release, beneficial during overnight recovery.[101] In addition, a high PDCAAS (protein digestibility-corrected amino acid score) or DIAAS (digestible indispensable amino acid score) is indicative of a protein's capacity to support muscle growth.[87] Therefore, an ideal protein source for hypertrophy should be rich in BCAAs, contain all EAAs, be highly digestible, and tailored to the timing of intake for optimal MPS stimulation.

Optimal Protein Requirements for Hypertrophy

Evidence indicates that a daily protein intake of 1.6 g/kg optimizes MPS in young adults engaged in resistance training, while older adults—due to anabolic resistance—should consume at least 1.2 g/kg/day to preserve muscle mass.[71] A meta-analysis from 2018 suggests that intakes exceeding 1.6 g/kg/day to 2.2 g/kg/day do not confer additional benefits for muscle mass gains, highlighting a physiological threshold in the hypertrophic response to protein intake.[65] Nevertheless, newer and quite popular evidence has emerged, where it is shown that there appears to be no upper limits to the anabolic response by protein ingestion, by testing 100 g against 25 g of protein in a single bolus. The 100 g protein proved superior in terms of whole-body protein net balance, muscular development, and plasma protein synthesis rates.[108] Even so, the fact that such upper limit has not yet been found does not warrant that higher protein intakes will necessarily offer the best cost/benefit in most cases. As protein is usually the most expensive nutrient, staying in the upper range of 1.6 g/kg/day to 2.2 g/kg/day will probably yield the best cost-benefit ratio for most athletes. If protein is easy and cheap to access, and all other factors have already been optimized (timing, other macronutrients, training, rest), there could be some room for exploring higher protein consumption rates.

Comparison Between Animal and Plant Proteins

The source of protein significantly affects hypertrophy due to differences in essential amino acid profiles and digestibility. Animal proteins (such as whey, casein, egg, and meat) are richer in leucine—a key activator of mTORC1. Leucine stimulates mTORC1 directly by inhibiting TSC2 and interacting with Rag GTPases, facilitating mTORC1 translocation to lysosomes where activation occurs.[14,92] Plant proteins (e.g., soy, rice, and pea) can elicit similar anabolic responses if consumed in sufficient amounts and combined to ensure a complete amino acid profile. However, due to lower digestibility and leucine content, it is recommended that plant-based proteins be ingested at 20% to 30% higher amounts to achieve effects comparable with those of animal proteins (this is particularly helpful regarding whole foods).[62,70,74] Under the summed weight of evidence, when equating for amino acidic content and digestibility, there is no significant difference between animal or plant proteins for general nutritional goals and for optimizing hypertrophy.

Protein Distribution and Timing

Beyond total daily protein intake, its distribution throughout the day is key to optimizing muscle anabolism. Research shows that spreading protein consumption across 3 to 4 meals, each delivering at least 0.4 to 0.5 g/kg of protein, maximizes mTORC1 activation and postprandial MPS.[5,120] Pre-sleep protein ingestion has gained attention as a strategic approach to enhance overnight MPS, particularly when paired with resistance training. Consuming 30 to 40 grams of slow-digesting protein, such as casein, before sleep has been shown to increase overnight amino acid availability and elevate MPS rates during sleep without negatively affecting fat metabolism or body composition.[46,101,102] Studies indicate that pre-sleep protein supports greater strength and hypertrophy gains when combined with consistent training, especially in trained participants over a multiweek period.[73] The anabolic benefit appears to be most effective when total daily protein intake is already sufficient, suggesting it acts as a complementary rather than essential strategy.[119]

Other Macronutrients: Carbohydrates and Fats

Role of Carbohydrates in Resistance Training

Carbohydrates are the primary and most efficient fuel source during high-intensity resistance training because they support rapid ATP regeneration through anaerobic glycolysis, which is crucial for sustaining repeated bouts of moderate to high-load efforts typical of hypertrophy-focused sessions.[37] During resistance exercise, intramuscular glycogen serves as the dominant substrate for ATP production, especially as set duration and session length increase. Maintaining adequate glycogen stores is therefore critical to preserving training volume, intensity, and total workload—all essential mechanical and metabolic stimuli for muscle hypertrophy.[73] When glycogen becomes depleted, performance often declines due to reduced energy availability and premature fatigue, leading to fewer effective repetitions, lower loads, and reduced training quality; this degradation in training capacity directly limits the mechanical tension and muscle fiber recruitment necessary for hypertrophic adaptations.[37] In addition, carbohydrates facilitate muscle glycogen resynthesis, and promote efficient recovery. Exercise-induced glycogen depletion compromises the muscle's contractile capacity and may impair the activation of anabolic pathways such as mTORC1, which is fundamental for protein synthesis.[58] Following a training session, the administration of carbohydrates

stimulates insulin release, enhancing glucose uptake by skeletal muscle and promoting the activation of protein kinase B (Akt)—a central mediator of anabolic signaling.[58,100] Carbohydrates also contribute to a more favorable hormonal environment by influencing insulin and thyroid hormone levels, which are indirectly supportive of muscle growth.[73] Ensuring consistent and sufficient carbohydrate intake should therefore be a cornerstone of hypertrophy-oriented nutrition strategies. Therefore, ensuring sufficient carbohydrate intake to sustain glycogen availability and support postexercise recovery should be considered a foundational strategy in resistance training programs aimed at maximizing muscle growth.

Carbohydrate Intake Timing

Strategic timing of carbohydrate intake around resistance training sessions can enhance performance, support recovery, and potentially optimize muscle growth. Pre-exercise carbohydrate consumption plays a key role in ensuring adequate glycogen availability, which is especially important during high-volume hypertrophy-focused sessions where energy demands are elevated. Consuming carbohydrates 1 to 3 hours before training helps maintain blood glucose levels and delays the onset of fatigue during prolonged or intense resistance workouts.[37,58] Intraworkout carbohydrates, though less critical for shorter sessions, may be beneficial during extended or 2-a-day training by providing an ongoing glucose supply, preserving performance, and reducing perceived exertion.[73] Postexercise carbohydrate intake is essential for replenishing depleted glycogen stores, especially when training sessions are separated by <24 hours or occur multiple times per day. Prompt glycogen restoration supports recovery and helps maintain subsequent training quality.[37,58] While protein is the primary macronutrient for stimulating MPS, carbohydrates support the recovery process by reducing muscle protein breakdown and facilitating an anabolic hormonal environment.[46]

Carbohydrate Needs for Gains

General recommendations for resistance-trained athletes targeting hypertrophy range from 3 to 6 grams of carbohydrates per kilogram of bodyweight per day, with higher intakes required during periods of elevated training volume or frequency.[99] When aiming to gain lean mass, carbohydrates are the most efficient and preferred macronutrient for increasing caloric intake due to their protein-sparing nature and ability to replenish glycogen stores, which are critical for sustaining high training volume and intensity.[100] A moderate energy surplus of approximately 200 to 500 kcal/day is often recommended to support muscle growth while minimizing fat gain.[73]

Fats and Hormonal Regulation

Fats play a crucial role in regulating hormonal levels and cellular function in skeletal muscle. Lipid intake modulates testosterone production—a key anabolic factor for hypertrophy—by influencing cholesterol synthesis and activating androgen receptors.[100] Diets containing <20% total fat have been shown to significantly reduce circulating testosterone levels, which compromises the muscle's ability to respond to resistance training.[118] Therefore, an adequate fat intake of 0.8 to 1.88 g/kg is recommended to maintain an optimal hormonal environment for athletes aiming to increase muscle mass.[117]

Fatty Acid Profile and Hypertrophic Response

The type of fats consumed also impacts the hypertrophic response. Omega-3 polyunsaturated fatty acids (2-4 g/day) have been demonstrated to modulate postexercise inflammation and enhance MPS by activating the Akt/mTOR pathway.[14,70] In addition, omega-3 supplementation has been linked to improved muscle mass retention in older adults and athletes performing high-intensity training.[112] In contrast, excessive intake of saturated fats can induce insulin resistance and disrupt anabolic signaling, thereby limiting the muscle's capacity to respond to hypertrophic stimuli.[58]

The key points covered in the nutrition section of this manuscript regarding protein, carbohydrate and fats intake, can be found in Figure 3.

Sleep and Recovery

As established throughout this review, sustained muscular hypertrophy is dependent on effective recovery. This section will examine the critical role of sleep as the cornerstone of the recovery process. This foundational component operates in concert with the specific training stimuli of frequency and repetition schemes, as well as the nutritional support required for cellular adaptation, to create the conditions necessary for long-term hypertrophic success.

Importance of Sleep

Sleep is a fundamental pillar for optimizing muscle hypertrophy due to its significant impact on the molecular regulation of protein metabolism, hormonal homeostasis, and muscle tissue recovery. Sleep deprivation and disruptions in circadian rhythms can impair MPS and promote a catabolic state that interferes with adaptations from resistance training.[63] Regarding sports performance, short-term sleep deprivation (e.g., 1 night) may not affect single-joint strength performance, but chronic sleep restriction reduces performance in multijoint lifts and impairs training quality.[45] Muscle protein synthesis is blunted, and protein breakdown is elevated during prolonged sleep loss.[21]

Sleep Duration and Muscle Growth

Adequate sleep (7-9 hours) is essential for optimizing muscle hypertrophy and strength development. Sleep restriction impairs muscle recovery, reduces anabolic hormone production (e.g., testosterone, growth hormone), and increases catabolic hormones such as cortisol.[16,45]

Circadian Regulation

The circadian system, governed by the suprachiasmatic nucleus (SCN) of the hypothalamus, controls multiple physiological processes, including skeletal muscle metabolism. Disruptions in

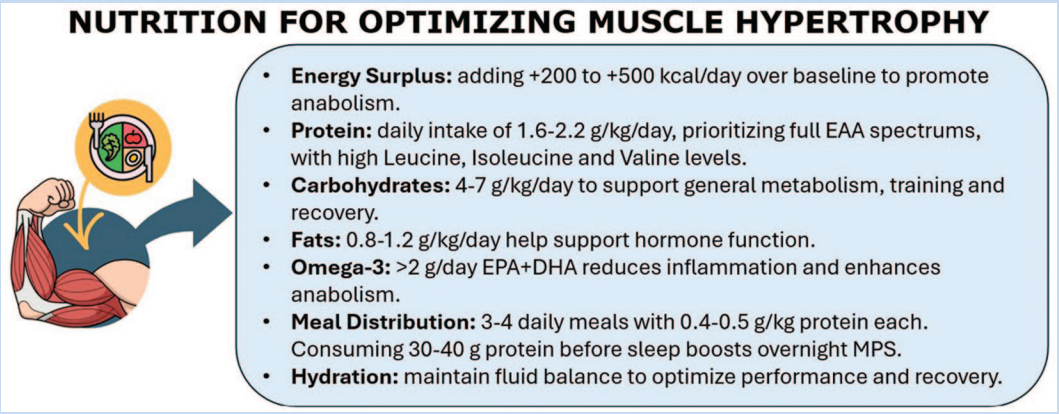


Figure 3. Summary of the key nutritional variables to consider to maximize MPS and muscle hypertrophy. The key aspects can be encompassed within proper protein, carbohydrate, and fat intake within a moderate caloric surplus. DHA, docosahexaenoic acid; EAA, essential amino acids; EPA, eicosapentaenoic acid; MPS, muscle protein synthesis.

circadian rhythms, whether through sleep deprivation or insufficient light exposure, disturb the expression of key genes such as *BMAL1* and *CLOCK*. These genes regulate the mTORc1 pathway, which is fundamental for muscle hypertrophy.[24,97] Moreover, circadian disruption reduces the efficiency of MPS and shifts energy utilization toward lipolysis rather than glycolysis during rest.[98] Inadequate SCN activation may also impair mitochondrial function and muscle regeneration, reducing resistance training effectiveness.

Hormonal Effects

Sleep quality directly influences the secretion of hormones that regulate muscle hypertrophy:

- Growth Hormone: secreted predominantly during deep nonrapid eye movement sleep, growth hormone facilitates tissue regeneration and activates the IGF-1/Akt/mTOR pathway, promoting protein synthesis and inhibiting muscle protein degradation.[63]
- Testosterone: peaks during rapid eye movement sleep; sleep restriction significantly lowers testosterone levels, which diminishes mTOR activation and reduces protein synthesis.[105]
- Cortisol: Chronic sleep deprivation increases cortisol levels, promoting a catabolic state by enhancing the ubiquitin-proteasome system, which in turn accelerates muscle protein degradation and limits hypertrophy.[97]

Protein Metabolism and Recovery

Adequate sleep promotes a balance between MPS and degradation. Proper sleep activates the mTORC1 pathway, which regulates muscle mRNA translation and phosphorylates ribosomal proteins to facilitate protein synthesis.[24] Conversely, lack of sleep stimulates activation of AMPK—an energy-sensing kinase that inhibits mTORC1 and promotes autophagy and muscle catabolism.

Consequences of Sleep Disruption

Even a single night of sleep deprivation can reduce MPS by 18%, indicating that even minor sleep quality disruptions can compromise muscular adaptation to training.[63] In addition, sleep fragmentation alters the postexercise inflammatory response, prolonging the protein degradation phase and impeding efficient muscle recovery.[63]

Improving Sleep and Recovery

Improving sleep quality is essential for maximizing recovery and hypertrophy, and several behavioral and environmental techniques have been shown to enhance sleep architecture. Maintaining a consistent sleep-wake schedule (even on weekends) helps regulate circadian rhythms, supporting better hormonal balance and sleep efficiency.[48] Reducing exposure to blue light from screens ≥1 hour before bed helps prevent suppression of melatonin - the hormone critical for sleep onset.[16] Creating a dark, cool, and quiet sleep environment further promotes restorative slow-wave sleep, which is linked to growth hormone release and muscle repair.[21] Engaging in mindfulness or relaxation techniques such as breathing exercises or meditation before bed can reduce sympathetic nervous system activity, improving sleep onset and depth.[45] Finally, athletes may consider pre-sleep protein ingestion (e.g., 30-40 g casein) to support overnight MPS without disrupting sleep quality.[102] Supplementation with melatonin and some micronutrients is also an effective aid for improving sleep quality.[27,40,41]

The key ideas associated with sleep and recovery in this manuscript can be found in Figure 4.

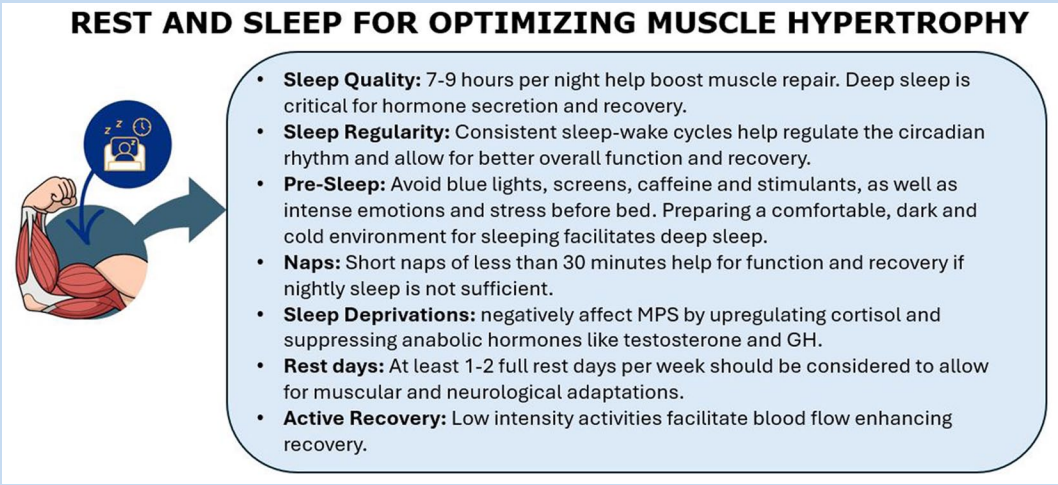


Figure 4. Summary of rest modalities and variables to optimize for maximizing muscle growth. Sleep emerges as the most important recovery modality, where ensuring sleep time, quality, and regularity are essential for effective recovery and function. GH, growth hormone; MPS, muscle protein synthesis.

DISCUSSION

The analysis of resistance training variables highlights that an appropriate balance of volume, intensity, frequency, and proximity to failure is critical for muscular hypertrophy adaptations. Advanced training techniques, such as drop sets and BFR, offer additional means to overcome training plateaus and further stimulate hypertrophic responses. Meanwhile, nutritional considerations (especially optimal protein intake in terms of quantity, quality, and timing) are vital to support MPS and overall anabolic signaling. Moreover, the role of carbohydrates and fats in fueling training efforts and regulating hormonal environments cannot be overstated.

Equally important is the emphasis on recovery, where adequate sleep and circadian regulation emerge as pivotal factors for maximizing training adaptations and preventing catabolic states. The convergence of these strategies not only benefits athletic performance but also holds significant implications for clinical populations and healthy aging.

Despite these advances, the current evidence is not without limitations. Many studies in this area feature relatively short intervention durations, small sample sizes, and heterogeneous populations, which can limit the generalizability of findings. In addition, the complex interactions among training variables, nutritional factors, and recovery modalities often rely on observational data and acute mechanistic studies rather than long-term, controlled interventions. There is a clear need for more robust, large-scale randomized controlled trials and longitudinal studies to better delineate cause-and-effect relationships and to account for individual variability, including age, sex, and genetic factors.

Practical Applications

This review underscores that optimizing muscle hypertrophy and strength involves a multifaceted approach, integrating tailored resistance training, precise nutritional strategies, and effective recovery protocols. The synthesis of current evidence reveals that the interplay of mechanical tension, metabolic stress, and molecular signaling, mediated primarily by pathways such as mTORC1 and modulated by factors such as myostatin inhibition and satellite cell activity, is central to driving muscular hypertrophy adaptations.

CONCLUSION

This narrative review advocates for an integrated, individualized approach that combines resistance training, nutritional optimization, and recovery enhancement. Future research should aim to refine these protocols further, employing rigorous study designs that explore the long-term effects of varied training and nutritional strategies. Such research will be crucial in addressing current limitations and advancing our understanding of how to maximize muscle hypertrophy and overall physical health.

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DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work the authors used Chat-GPT to improve translations and writing. Google's Gemini was used

for initial crafting of some images. After using these tools, the authors reviewed and edited the content as needed. The authors take full responsibility for the content of the published article.

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