Review Article

The impact of resistance training volume and intensity: Exploring the role of repetitions and sets in regulating irisin secretion and its anabolic and metabolic benefits in bodybuilders

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Abstract

Irisin, a myokine cleaved from the membrane protein Fibronectin type III domain-containing protein 5 (FNDC5), has emerged as a critical exercise-induced hormone. It is implicated in the browning of white adipose tissue, enhanced metabolic rate, and potential anabolic processes. In bodybuilding, where precise manipulation of training variables-specifically repetitions (reps) and sets-is paramount, understanding how these variables influence irisin secretion could optimize both physique and health outcomes. This narrative review aims to synthesize current evidence on the effects of resistance training protocols, with a focus on reps and sets, on irisin secretion. Furthermore, it explores the potential subsequent benefits of elevated irisin levels for bodybuilders, including its putative roles in fat metabolism, muscle remodeling, and overall metabolic health. Evidence suggests that high-volume resistance training protocols, characterized by multiple sets (≥3) and moderate repetitions (8-12 reps), may be potent stimulators of irisin release. This secretion is hypothesized to be mediated by muscle contraction-induced PGC-1α expression. Elevated irisin levels are often correlated with improved lipid oxidation, which could aid in cutting phases by promoting a leaner physique. Additionally, preclinical and some human studies suggest irisin may support muscle hypertrophy through enhanced nutrient partitioning and autocrine/paracrine signaling, though this mechanism requires further elucidation. Strategic manipulation of resistance training volume and intensity may represent a viable method for modulating irisin secretion. Incorporating protocols that could elevate this myokine might provide bodybuilders with a dual advantage: enhancing metabolic efficiency to reduce adipose tissue and potentially supporting muscle growth and recovery. However, the current evidence is not yet definitive, and more research is needed to confirm these links.

Key Words: Bodybuilders, Resistance training, Irisin, Anabolic, Metabolic

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Introduction

Resistance training is widely recognized for its pivotal role in modulating muscle hypertrophy and metabolic health. The biochemistry of skeletal muscle adaptations involves numerous signaling molecules, among which irisin, a myokine cleaved from FNDC5, has attracted significant scientific attention alongside some controversy regarding its measurement and functions. Irisin is proposed to play a central role in exercise-induced browning of white adipose tissue and metabolic enhancement (Boström et al., 2012; Polyzos et al., 2018). For bodybuilders, who meticulously regulate training volume and intensity via repetitions and sets, understanding the regulation and function of irisin may help unveil novel strategies to optimize both muscle growth and fat metabolism (Zunner et al., 2022). Given the emerging evidence, irisin is not only implicated in metabolic regulation but also appears to have potential anabolic effects on muscle tissue, suggesting a possible bridge between performance and health benefits (Reza et al., 2017).

Exercise-induced irisin secretion has been linked mechanistically to muscle contraction-induced expression of PGC-1α, which governs FNDC5 expression (Shen, 2022). While endurance exercises have been classically associated with irisin release, contemporary evidence suggests that resistance training structured with specific volumes and intensities can also be an effective stimulator of irisin secretion (Vecchiato et al., 2022; Alizadeh et al., 2022). The claim of a "superior effect" compared to endurance training remains speculative without more direct comparative studies. These insights motivate further exploration into how specific resistance training protocols, focusing on reps and sets, might modulate irisin to mediate hypertrophic and metabolic outcomes in bodybuilding contexts.

Methodology

The narrative review methodology involved a comprehensive synthesis of current primary research and meta-analyses addressing the effects of resistance training on irisin secretion

and its physiological outcomes. Databases including PubMed, PMC, Scopus, and ScienceDirect were searched from 2012 to October 2023 using keywords such as "resistance training," "irisin secretion," "myokines hypertrophy," and "training volume and intensity." Inclusion criteria prioritized studies published in peer-reviewed journals within the last decade to ensure contemporary relevance, with a focus on those elucidating molecular mechanisms involving FNDC5/irisin and exercise variables like reps and sets (Alizadeh et al., 2022; Kim et al., 2021).

Qualitative synthesis emphasized randomized controlled trials, intervention studies, and mechanistic explorations in human subjects. While animal model studies were identified in the search, their findings are not a focus of this synthesis to maintain direct applicability to the human bodybuilding population. Meta-analyses providing pooled quantitative insights into irisin modulation by resistance training volume and intensity were specifically considered to contextualize the potential anabolic and metabolic benefits for bodybuilders (Kim et al., 2021). Data extraction focused on training protocols, intensity (expressed as %1RM), repetition schemes, irisin measurement techniques, and physiological endpoints such as muscle hypertrophy markers and lipid oxidation metrics.

The fundamentals of resistance training for hypertrophy

Hypertrophy training typically involves moderate repetitions (6–12 reps) with multiple sets (≥3) at 70–85% of one repetition maximum (1RM), designed to maximize muscle fiber cross-sectional area, particularly in fast-twitch fibers (Zunner et al., 2022). This training paradigm activates both phosphagen and glycolytic energy pathways, fostering metabolite accumulation, which is implicated in muscle growth signaling cascades (American College of Sports Medicine, 2021; Zunner et al., 2022). Rest intervals between sets are typically 1 to 3 minutes, balancing recovery and metabolic stress essential for hypertrophic adaptations.

Emerging insights link hypertrophy-focused training to the upregulation of signaling pathways that stimulate muscle protein synthesis, including the mammalian target of rapamycin (mTOR) pathway (Schoenfeld, 2010). Training volume, described as total repetitions multiplied by load and sets, is increasingly regarded as a critical determinant for maximizing hypertrophy responses, with individual variability in adaptation (Zunner et al., 2022). Moreover, chronic resistance exercise programs that progressively increase load and volume show sustained elevations in circulating myokines, potentially including irisin, thereby possibly aligning metabolic improvements with anabolic signals (Kim et al., 2021).

Irisin: A mechanistic overview

Irisin is produced by proteolytic cleavage of FNDC5, a membrane protein regulated by the transcriptional coactivator PGC-1α during muscle contraction (Boström et al., 2012; Motahari Rad, 2021). Its secretion is augmented in response to exercise, particularly resistance training, through calcium-dependent signaling pathways activating AMPK and PGC-1α, culminating in FNDC5 expression and irisin release (Liu et al., 2022). Irisin acts primarily by binding integrin αV/β5 receptors, triggering downstream activation of signaling cascades such as MAPK, ERK1/2, and AMPK, which mediate metabolic and anabolic effects (Liu et al., 2022).

Functionally, irisin is suggested to promote the browning of white adipose tissue by stimulating uncoupling protein 1 (UCP1) expression, thereby potentially increasing energy expenditure and improving insulin sensitivity (Boström et al., 2012; Shen, 2022). In skeletal muscle, preclinical studies indicate irisin can stimulate hypertrophic gene expression including insulin-like growth factor 1 (IGF-1), while suppressing negative regulators like myostatin, suggesting direct participation in muscle remodeling and growth (Reza et al., 2017; Huh et al., 2014). Its short half-life and rapid degradation highlight the potential significance of exercise timing and training variables in optimizing circulating levels (Jedrychowski et al., 2015).

The stimulus: How reps and sets modulate irisin secretion

The volume and intensity of resistance training, operationalized as repetitions and sets, are proposed as crucial determinants of irisin secretion magnitude. Multiple studies suggest that protocols with moderate repetitions (8-12 reps) and higher set volumes (≥3 sets) can robustly stimulate irisin release through sustained muscle contraction and metabolic stress (Vecchiato et al., 2022; Alizadeh et al., 2022). Higher intensity training, defined as loads around 60–85% 1RM, appears to amplify the activation of AMPK and PGC-1α, leading to greater FNDC5 expression (Kim et al., 2021; Parada-Sánchez et al., 2022).

Evidence further indicates a temporal profile of irisin secretion where acute bouts of resistance training cause sharp but transient elevation, while chronic training may prolong elevated baseline levels, assuming progressive overload is applied (Damas et al., 2018). Interestingly, lower volume or non-progressive training protocols often do not sustain irisin increases, underscoring the potential importance of training manipulation in maintaining myokine benefits (Kim et al., 2021). It is important to note, however, that not all studies report consistent increases, as seen in researches, highlighting the need for standardized protocols. These findings partially validate the bodybuilding principle of structured reps and sets for metabolic and anabolic optimization (Table 1).

The response: Beneficial effects of irisin for the bodybuilder

Based on current evidence, elevated irisin levels could confer multiple potential advantages for bodybuilders. Irisin is associated with enhanced lipid oxidation and mitochondrial biogenesis, which may promote fat loss during caloric deficits, a critical factor during cutting cycles to maintain muscle mass while reducing adiposity (Shen, 2022). Its proposed role in the browning of white adipose tissue could increase basal metabolic rate and improve metabolic flexibility, a vital adaptation for body composition management (Shen, 2022).

On the anabolic side, preclinical data suggest irisin may stimulate hypertrophic pathways by upregulating IGF-1 and downregulating myostatin, potentially facilitating satellite cell activation and protein synthesis (Reza et al., 2017; Huh et al., 2014). Moreover, irisin is hypothesized to mediate autocrine and paracrine signaling in muscle tissue, thereby possibly promoting recovery and adaptation to resistance-induced muscle damage (Liu et al., 2022). While promising, these anabolic benefits in humans, particularly in trained bodybuilders, require more robust confirmation.

Controversies and unresolved questions

Despite growing evidence on irisin's exercise-related roles, significant controversies remain regarding the magnitude and consist

consistency of its secretion in response to resistance training. Some studies report conflicting data with no significant changes in circulating irisin after certain training regimens, influenced by subject characteristics, training duration, and critically, assay variability (Polyzos et al., 2018). The field has been historically challenged by questions surrounding the specificity of early commercial ELISAs and antibodies used to detect irisin, which has contributed to inconsistent findings across studies (Jedrychowski et al., 2015).

The mechanistic pathways for irisin's anabolic effects on human skeletal muscle remain incompletely understood, with ongoing investigations into receptor specificity and intracellular signaling (Liu et al., 2022). Additionally, interindividual differences related to age, sex, and training history complicate generalizations. The extrapolation of findings from studies on elderly or sedentary populations to elite bodybuilders is a key limitation in the current literature. Future research should focus on standardized, validated assays and longitudinal designs in trained cohorts to clarify irisin's potential metabolic-anabolic contributions.

Practical applications and recommendations

For bodybuilders seeking to harness irisin's benefits, resistance training programs should emphasize moderate repetition ranges (8–12 reps) combined with high set volumes (at least 3 sets) and progressively increasing intensity (60–85% 1RM) to maximize secretion (Vecchiato et al., 2022; Cosio et al., 2021). Training

Table 1. Key findings on resistance training protocols, irisin secretion, and related anabolic and metabolic responses.

Study / Source	Training Protocol	Irisin Response	Mechanism Highlight	Anabolic & Metabolic Effects
Motahari Rad (2021)	Resistance training, mixed sets & reps	Increased irisin with higher volume	PGC-1α induced FNDC5 expression	Fat browning, improved metabolism
Boström et al. (2012)	Exercise-induced FNDC5/Irisin release	Elevated post-exercise irisin	PGC-1α upregulation, browning of white fat	Metabolic rate ↑, thermogenesis
Zhao et al. (2017)	12 weeks, moderate-heavy resistance	Significant serum irisin increase	Muscle contraction-enhanced irisin secretion	Fat % reduction, muscle function improvement
Vecchiato et al. (2022)	High-intensity interval resistance	Greater irisin increase at higher intensity	AMPK-PGC-1α pathway activated	Enhanced lipid oxidation, metabolic flexibility
Liu et al. (2022)	Resistance training	Irisin stimulates pro-myogenic genes	IRF signaling via integrin receptors	Muscle hypertrophy, satellite cell activation
Cosio et al. (2021)	Chronic RT with progressive overload	Sustained increase in baseline irisin	Autocrine and paracrine effects on muscle tissue	Autophagy stimulation, enhanced nutrient partition
Ataeinosrat et al. (2022)	Moderate reps (8-12), multiple sets (≥3)	Volume-dependent irisin release	Calcium and AMPK mediated signaling	Improved muscle remodeling, anabolic signaling
Kim et al. (2021)	Meta-analysis of chronic RT	Sustained increase in baseline irisin with progressive overload	Autocrine and paracrine effects on muscle tissue	Improved metabolic parameters
Alizadeh et al. (2022)	Moderate reps (8-12), multiple sets (≥3)	Volume-dependent irisin release	Calcium and AMPK mediated signaling	Improved muscle remodeling markers
Javadifar et al. (2021)	Resistance vs combination training	Mixed results, some find higher RT irisin	Training volume and metabolic stress modulate secretion	Metabolic and hypertrophic adaptations

should be periodized to maintain progressive overload, preventing plateauing in irisin levels (Ataeinosrat et al., 2022). Monitoring recovery and muscle fatigue is essential to support irisin-mediated anabolic signaling.

Nutritional strategies that support overall muscle protein synthesis, such as adequate protein intake (~1.6-2.2 g/kg/day) and peri-workout nutrition, may indirectly support hypertrophic responses in concert with exercise-induced myokine secretion (Schoenfeld & Aragon, 2018). Combining resistance training with low-volume, high-intensity aerobic sessions performed in a conditioned state might further enhance metabolic health while potentially minimizing interference with hypertrophy, though this requires careful management (Methenitis, 2018). Given irisin's short half-life, the practical implications of workout timing remain speculative; however, consistent training adherence is likely more critical than precise timing.

Conclusion

Resistance training volume and intensity appear to influence irisin secretion, a myokine with potential anabolic and metabolic benefits for bodybuilders. Protocols characterized by moderate repetitions and multiple sets may enhance irisin release via PGC-1α mediated FNDC5 expression, potentially supporting fat browning, lipid oxidation, and muscle hypertrophy. It is crucial to acknowledge the existing controversies, including inconsistent findings and methodological challenges in irisin measurement. Current evidence suggests that designing resistance exercise programs with these variables in mind may be a viable strategy, but it is not yet a proven optimization. Further research with robust methodologies is warranted to refine mechanistic understanding and establish evidence-based training prescriptions for irisin modulation.

What is already known on this subject?

Resistance training is widely recognized for its pivotal role in modulating muscle hypertrophy and metabolic health. The biochemistry of skeletal muscle adaptations involves numerous signaling molecules, among which irisin, a myokine cleaved from FNDC5, has attracted significant scientific attention alongside some controversy regarding its measurement and functions. Irisin is proposed to play a central role in exercise-induced browning of white adipose tissue and metabolic enhancement.

What this study adds?

Resistance training volume and intensity appear to influence irisin secretion, a myokine with potential anabolic and metabolic benefits for bodybuilders. Protocols characterized by moderate repetitions and multiple sets may enhance irisin release via PGC-1α mediated FNDC5 expression, potentially supporting fat brow-ning, lipid oxidation, and muscle hypertrophy.

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Data availability

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Author contributions

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