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Overcoming Post-Operative Anabolic Resistance: The Integrated Role of Protein Nutrition and Physical Rehabilitation in Orthopedic Patients

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ABSTRACT

Introduction: Orthopedic surgery and subsequent disuse trigger a severe systemic stress response. This hostile environment induces anabolic resistance. Consequently, skeletal muscle loses its sensitivity to nutritional inputs and mechanical loading. At the molecular level, the process is driven by a failure of the mTORC1 signaling pathway and accelerated FOXO-mediated proteolysis. Ultimately, these mechanisms cause rapid muscle atrophy, a negative nitrogen balance, and functional decline.

Aim: The aim of this narrative review is to examine the molecular and physiological mechanisms of post-operative anabolic resistance and to evaluate how perioperative protein nutrition and mechanical loading combine to restore functional capacity in orthopedic patients.

Material and methods: This study was conducted as a narrative review of literature addressing the pathophysiology of post-operative anabolic resistance and integrated recovery strategies in orthopedic patients. A comprehensive literature search was performed using the

electronic databases PubMed/MEDLINE, Scopus, Web of Science, the Cochrane Library, and Google Scholar.

Results: Post-operative anabolic resistance represents a failure of the mTORC1 signaling path, elevating the leucine threshold needed for net muscle balance. Mechanical loading during rehabilitation acutely enhances muscle sensitivity to amino acids. Consequently, clinical outcomes are optimized when elevated, leucine-rich protein doses (30–40 g/meal, totaling 1.2–2.0 g/kg/day) are evenly distributed. Compared to integrated interventions, standalone nutritional or mechanical protocols exhibit significant variability in their functional endpoints.

Conclusions: Post-operative muscle loss is a multi-factorial process requiring a multidisciplinary approach. Overcoming anabolic resistance and accelerating recovery requires fully integrating nutrition into orthopedic rehabilitation, rather than treating it as an isolated intervention.

Keywords: anabolic resistance; orthopedic surgery; protein nutrition; leucine; muscle protein synthesis; physical rehabilitation.

1. INTRODUCTION

Skeletal muscle is not merely a structural tissue dedicated to locomotion.Moreover it functions as a metabolically active organ that plays a crucial role in systemic balance and substrate utilization. It is essential for metabolic homeostasis, glucose disposal, and systemic nitrogen storage. In physiological conditions, muscle mass is regulated by the balance between muscle protein synthesis (MPS) and muscle protein breakdown (MPB).Those processes are tightly controlled by nutrient availability and mechanical stimuli .Dietary protein ingestion provides the necessary structural substrates required for cellular remodeling and tissue repair. Concurrently, it acts as a potent biochemical anabolic trigger, primarily operating through the phosphorylation and subsequent activation of the mechanistic target of rapamycin complex 1 (mTORC1) signaling cascade [1]. In a healthy metabolic state, mechanical loading and dietary protein intake operate synergistically in order to preserve muscle mass.

Major orthopedic surgery, however, disrupts this balance. Surgical intervention inflicts significant local tissue trauma, which triggers a profound, systemic stress response. This neuroendocrine cascade is characterized by the hypersecretion of catabolic hormones (such as cortisol and catecholamines), an acute-phase immunological reaction, and the systemic release of pro-inflammatory cytokines [2]. This hostile metabolic environment shifts the body's priority toward survival and wound healing at the expense of musculoskeletal integrity. Moreover it leads to increased muscle loss, with immobilization contributing to declines of 0.5–1% muscle mass per day in the early postoperative phase [3]

Crucially, the primary pathophysiological driver behind this rapid, long-term wasting is a clinical phenomenon known as anabolic resistance. This state is defined as a severe, acute reduction in the sensitivity and responsiveness of skeletal muscle tissue to both hyperaminoacidemia and mechanical stimuli [4]. Consequently, standard dietary protein intake and conventional, low-intensity rehabilitation protocols, which would typically sustain a healthy individual, become profoundly insufficient to prevent postoperative muscle loss.

Therefore, the aim of this review is to reframe post-operative recovery by focusing on perioperative nutrition and physical rehabilitation not as isolated strategies, but as synergistic therapeutic pillars essential for overcoming anabolic resistance and restoring functional capacity in orthopedic patients.

2. MOLECULAR MECHANISMS: THE ROLE OF LEUCINE AND mTORC1

Skeletal muscle mass is maintained through the coordinated regulation of muscle protein synthesis (MPS) and muscle protein breakdown (MPB). These regulatory mechanisms converge on the mechanistic target of rapamycin complex 1 (mTORC1), which is a serine/threonine protein kinase situated downstream of the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway [1]. The activation of mTORC1 is a multiphase process that requires both hormonal and nutritional stimuli. Specifically, essential amino acids such as leucine initiate the translocation of mTORC1 to the lysosomal membrane via Rag GTPases. At this location, the complex interacts with the small GTPase Rheb to trigger its kinase activity [5]. Upon activation, mTORC1 phosphorylates the ribosomal protein S6 kinase 1 (p70S6K1) and the eukaryotic initiation factor 4E-binding protein 1 (4E-BP1). These

phosphorylation events promote mRNA translation and directly increase the rate of myofibrillar protein synthesis [6].

Simultaneously, the PI3K-Akt signaling axis serves as a critical negative regulator of protein degradation by inhibiting the ubiquitin-proteasome system. Under physiological conditions, Akt-mediated phosphorylation leads to the cytosolic sequestration of the Forkhead box O (FOXO) transcription factors. This sequestration prevents their nuclear translocation and the subsequent activation of proteolytic genes [7]. However, in states of surgical stress, systemic inflammation, or immobilization, the suppression of this axis allows FOXO to enter the nucleus. This translocation up-regulates the expression of muscle-specific E3 ubiquitin ligases, specifically MuRF-1 (Muscle RING-finger protein-1) and Atrogin-1 (MAFbx) [8]. These ligases are essential for inducing myofibrillar protein ubiquitination while concurrently inhibiting protein synthesis resulting in muscle loss.

The convergence of blunted mTORC1 activity and accelerated FOXO-mediated proteolysis characterizes the state of anabolic resistance. This condition increases the leucine threshold required to maintain net protein balance in post-operative patients [4]. Such a mechanistic understanding directly supports clinical recommendations for higher per-meal protein doses during recovery. Nevertheless, the translation of mTORC1 signaling responses to clinical functional outcomes remains incompletely characterized in post-operative populations.

3. THE SURGICAL STRESS RESPONSE AND PATHOPHYSIOLOGY OF ANABOLIC RESISTANCE

The primary etiology of post-operative muscle depletion is the systemic surgical stress response. Surgical intervention creates major physiological trauma, acting as a catalyst for localized pro-inflammatory cytokine release and sensory afferent signaling. This trauma induces activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system. The neuroendocrine cascade triggers a shift in endocrine, hemodynamic, and immunological domains, all directed toward the restoration of homeostasis [2].

This neuroendocrine activation modulates metabolism to prioritize catabolism. The resulting hormonal environment promotes a hypermetabolic state, characterized by the deleterious mobilization of energy reserves at the expense of structural integrity. This manifests as hyperglycemia, arising from systemic insulin resistance and increased hepatic

gluconeogenesis [9]. To satisfy this metabolic demand, both lipolysis and myofibrillar proteolysis are significantly up-regulated.

Skeletal muscle functions as the primary endogenous reservoir for amino acids during this catabolic phase. Protein degradation provides a sustained efflux of amino acids into the systemic circulation. These molecules serve as precursors for gluconeogenesis to maintain metabolic stability. Furthermore, this amino acid liberation supports the hepatic synthesis of acute-phase proteins, such as fibrinogen, which are essential for wound healing and immune function [2]. Clinically, this mandatory substrate redistribution results in a rapid decline in lean body mass and a persistent negative nitrogen balance. Consequently, skeletal muscle tissue is depleted to facilitate the metabolic requirements of surgical recovery.This metabolic disturbance is further escalated by release of pro-inflammatory cytokines, specifically interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). These mediators stimulate muscle protein breakdown (MPB) while simultaneously attenuating muscle protein synthesis (MPS). This imbalance leads to anabolic resistance, a clinical condition in which skeletal muscle becomes less responsive to amino acid intake and mechanical loading [4].

As established in the previous section, anabolic resistance represents a fundamental failure of the mTORC1 signaling axis. Under surgical stress and disuse, the muscle's sensitivity to leucine-mediated Rag GTPase activation is impaired. A prevailing misconception in clinical literature states that the resulting disuse atrophy is driven entirely by hyperactive kinetics of MPB. However, some data indicates that while an acute spike in MPB occurs post injury, the primary kinetic driver of long-term wasting is a negative net protein balance area under the curve (AUC). This deficit is mediated primarily by a severe depression of MPS and a blunted anabolic response to amino acid availability. [10] This defect implies that even with high amino acid availability, the desensitized mTORC1 complex fails to initiate effective mRNA translation, while the concurrent suppression of the PI3K-Akt axis facilitates the nuclear translocation of FOXO transcription factors, further accelerating the expression of E3 ubiquitin ligases.

Physical immobilization and advanced age further compound this impaired anabolic responsiveness. Disuse rapidly suppresses MPS and impairs amino acid transport into muscle cells [11]. Systematic evidence indicates that even short-term immobilization leads to significant muscle atrophy despite adequate nutritional intake, underscoring the dominant role of mechanical unloading in driving resistance [12]. Importantly, anabolic resistance is not

solely induced by surgical stress and disuse but is further amplified by age-related impairments in muscle protein metabolism. Older adults demonstrate an even more pronounced blunting of the postprandial MPS response due to impaired intracellular signaling [13]. Collectively, these converging mechanisms result in a markedly elevated anabolic threshold.

4. REHABILITATION AND MECHANICAL LOADING IN ORTHOPEDIC PATIENTS

Physical rehabilitation is the core of functional recovery following orthopedic surgery. The mechanical loading represents the primary stimuli for restoration of skeletal muscle mass and strength. Resistance-based exercise promotes muscle protein synthesis (MPS) through activation of anabolic signaling pathways, including mechanistic target of rapamycin complex 1 (mTORC1), thereby counteracting disuse-induced muscle atrophy and functional decline [11].

A key feature of resistance exercise is the acute enhancement of anabolic responsiveness to amino acid availability following mechanical loading. This phenomenon reflects an increase in the efficiency of translational signaling, resulting in greater stimulation of myofibrillar protein synthesis in the post-exercise period when compared to resting conditions [14]. Although originally demonstrated in healthy individuals, this mechanism is considered fundamental for post-operative rehabilitation, where restoring anabolic sensitivity is a critical determinant of recovery.

However, the adaptive capacity of skeletal muscle is significantly impaired under conditions of disuse, surgical stress, and aging. Immobilization induces rapid reductions in basal MPS, decreases muscle cross-sectional area, and impairs neuromuscular function even over short time periods [3]. In parallel, older adults exhibit a pronounced reduction in muscle protein synthetic responsiveness to anabolic stimuli, including both dietary protein and exercise, further exacerbating the effects of disuse [15].Beyond muscle mass regulation, rehabilitation must also address neuromuscular control, balance, and proprioception, which are critical determinants of functional stability and safe return to activity. Systematic evidence demonstrates that neuromuscular training improves postural control and dynamic stability, and contributes to reduced risk of recurrent musculoskeletal injury following lower-limb

injury [16]. These adaptations are particularly relevant in orthopedic populations, where deficits in sensorimotor control persist beyond initial structural recovery.

Importantly, disuse and immobilization are associated with profound impairments in neuromuscular function, which cannot always be fully reversed by conventional rehabilitation alone. Experimental and clinical data indicate that neuromuscular decline following immobilization is only partially restored through standard loading protocols, suggesting the need for multimodal interventions targeting both mechanical and metabolic pathways [17].

In this context, rehabilitation should be understood as a graded intervention spanning early mobilization, progressive resistance training, and neuromuscular re-education. While mechanical loading is essential for restoring contractile function and muscle mass, its effectiveness is constrained under conditions of anabolic resistance. Therefore, optimal recovery requires integration with metabolic support strategies that restore anabolic responsiveness and support tissue remodeling[11,3].

5. NUTRITIONAL STRATEGIES AND PROTEIN METABOLISM IN ORTHOPEDIC PATIENTS

Nutritional intervention represents a central determinant of recovery following orthopedic surgery, particularly in the context of disuse-induced anabolic resistance. Preoperative nutritional optimization (prehabilitation) has been shown to enhance metabolic resilience and improve postoperative recovery trajectories. Increasing protein intake to approximately 1.6 g/kg/day prior to surgery may attenuate postoperative muscle loss and improve recovery of lean mass[18,19]. Following surgery, protein requirements are substantially elevated due to increased catabolic signaling, inflammation, and negative nitrogen balance. Orthopedic guidelines generally recommend intakes of 1.2–2.0 g/kg/day, with higher requirements in patients with severe trauma, prolonged immobilization, or frailty [3].

A major determinant of postoperative nutritional efficacy is anabolic resistance. This condition necessitates higher per-meal protein doses approximately 30–40 g to stimulate muscle protein synthesis effectively[20]. This phenomenon is particularly pronounced in older orthopedic patients, where impaired intracellular signaling further elevates the anabolic threshold. Beyond total daily intake, protein distribution and timing are critical modulators of anabolic efficiency. Evenly distributed protein intake across meals enhances 24-hour muscle protein synthesis compared to skewed intake patterns[21]. Moreover, aligning protein

ingestion with periods of heightened anabolic sensitivity further enhances amino acid utilization and supports muscle remodeling [22]. Pre-sleep protein intake has additionally been shown to stimulate overnight protein synthesis and improve net protein balance during recovery [23].Protein quality is another critical factor influencing anabolic response. Leucine-rich proteins such as whey protein more effectively stimulate MPS due to their superior ability to activate mTORC1 signaling pathways [1,24]. This is particularly relevant under conditions of anabolic resistance, where higher leucine availability is required to overcome impaired intracellular signaling.

Complementary nutritional strategies may further enhance muscle preservation during periods of immobilization. β-hydroxy β-methylbutyrate (HMB) has been identified as a clinically relevant anti-catabolic agent that reduces muscle protein breakdown during disuse conditions [20]. In addition, perioperative strategies aimed at avoiding prolonged fasting and maintaining even minimal nutrient availability have been shown to attenuate activation of proteolytic pathways and reduce surgical catabolism [25].Experimental evidence further supports the metabolic benefits of preoperative nutritional intervention. Short-term hypocaloric feeding with glucose and amino acids prior to surgery can attenuate activation of the ubiquitin–proteasome system and reduce surgical catabolism, even when total caloric intake is limited [25]. This suggests that metabolic signaling rather than caloric load per se is a key determinant of perioperative muscle preservation.

Finally, micronutrient status may influence anabolic efficiency. Vitamin B6 (pyridoxine) plays a key role in amino acid metabolism and nitrogen transfer, and deficiencies may impair protein synthesis capacity. This reinforces the need for comprehensive perioperative nutritional strategies addressing both macro- and micronutrient adequacy [19].

Despite strong mechanistic and clinical evidence, implementation of nutritional strategies in orthopedic practice remains inconsistent due to variability in clinical protocols, resource limitations, and incomplete integration with rehabilitation pathways. This highlights the need for standardized, multidisciplinary approaches combining nutrition and rehabilitation as co-dependent components of recovery rather than isolated interventions.

6. Clinical Outcomes and Functional Recovery

Functional recovery following orthopedic surgery is ultimately defined by the restoration of physical performance and independence. Typically can be assessed through objective measures of mobility, strength, and validated patient-reported outcome measures (PROMs). These integrate the combined effects of surgical stress, nutritional status, and rehabilitation exposure, but do not directly reflect underlying mechanistic processes.

Across clinical studies, perioperative protein supplementation is associated with small-to-moderate improvements in functional outcomes, including gait speed, mobility indices, and self-reported recovery scores [22,26]. However, the results are inconsistent, suggesting substantial inter-individual variability in responsiveness to nutritional interventions.Importantly, nutritional status is a strong predictor of postoperative outcomes in orthopedic populations. Markers of malnutrition, including hypoalbuminemia and lymphopenia, are independently associated with increased risk of complications such as periprosthetic joint infection and mortality following major orthopedic surgery [20]. These findings highlight the clinical relevance of systematic nutritional assessment as part of perioperative management.

A consistent determinant of postoperative functional trajectory is baseline muscle quality. Higher preoperative muscle quality is associated with faster recovery of mobility and superior functional performance following major orthopedic procedures, particularly total joint arthroplasty [27]. These findings are reinforced by large population data demonstrating that reduced muscle quality is associated with higher risk of adverse health outcomes, including functional decline and loss of independence [28].

Importantly, the relationship between protein supplementation and functional outcomes appears context-dependent. Meta-analytic evidence indicates that improvements in muscle mass and strength are more pronounced when protein intake is combined with structured physical loading, whereas isolated nutritional strategies produce more variable effects on functional endpoints [29]. This supports the interpretation that nutritional interventions act as modulators of recovery capacity rather than independent drivers of functional restoration.

7.Limitations and challenges of Protein Supplementation

Despite a rapidly expanding body of literature supporting the role of perioperative protein nutrition in mitigating post-operative muscle loss, several methodological, translational, and clinical limitations constrain the direct application of these findings in orthopedic practice.

First, a large proportion of evidence comes from studies in healthy, young, or non-surgical populations. These models do not fully reflect the metabolic stress of surgery, which includes systemic inflammation, hormonal dysregulation, and reduced anabolic sensitivity. As a result, external validity for orthopedic patients is limited[3,30].

Second, there is significant heterogeneity in study design, including differences in protein dose, timing, amino acid composition, and rehabilitation protocols. This variability makes it difficult to define standardized clinical guidelines for optimal protein supplementation in surgical populations [29].

Third, many studies are limited by small sample sizes and short follow-up periods. Most focus on short-term outcomes such as lean mass or strength, while long-term functional outcomes (e.g., return to activity, sustained mobility) are underrepresented[26]

Fourth, real-world implementation is challenging. Post-operative patients often struggle to meet high protein targets due to reduced appetite, gastrointestinal symptoms, pain, or hospital constraints. Adherence to structured timing strategies is also inconsistent without multidisciplinary support [31].

Finally, there is strong individual variability in anabolic response. Age, baseline muscle mass, inflammation, and metabolic health influence sensitivity to protein intake. Older adults, in particular, exhibit anabolic resistance, requiring higher protein doses to achieve comparable muscle protein synthesis responses [13, 4].

Overall, while protein supplementation is a well-supported adjunct in orthopedic recovery, its effectiveness is context-dependent. Future research should focus on standardized protocols, longer follow-up, and personalized nutrition-rehabilitation strategies in surgical populations.

8. CONCLUSIONS

Post-operative skeletal muscle loss following orthopedic surgery is driven by the convergence of surgical stress, systemic inflammation, immobilization, and age-related anabolic resistance. These factors collectively impair mTORC1-mediated muscle protein synthesis while simultaneously enhancing proteolytic signaling, resulting in a persistent negative muscle protein balance. Current evidence supports a model in which mechanical loading through rehabilitation and dietary protein availability act as co-dependent regulators of recovery. Resistance exercise enhances anabolic sensitivity to amino acids and transiently upregulates translational efficiency, while protein intake provides the necessary substrate and signaling activation required to sustain muscle protein synthesis. This interaction is mechanistically consistent with established evidence on exercise-induced enhancement of amino acid utilization and MPS responsiveness.

Importantly, clinical outcomes are optimized when total protein intake is sufficient, distributed appropriately across the day, and aligned with periods of increased anabolic sensitivity such as post-rehabilitation sessions. In this context, protein quality (e.g., leucine-rich sources) and dose per feeding episode become particularly relevant under conditions of anabolic resistance.

Overall, the strongest available evidence supports the implementation of perioperative nutritional strategies—combined with progressive rehabilitation—as an integrated standard of care in orthopedic recovery. However, the field still requires large-scale, well-controlled clinical trials in surgical populations to define optimal protein dosing algorithms and to establish personalized nutrition-rehabilitation frameworks.

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Artificial Intelligence use declaration

AI tools were used only to refine the language and improve text readability. The authors retain full accountability for the academic integrity of the work. The conceptual design, literature review, data analysis, and final drafting were executed solely by the authors.

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