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Essential Amino Acid Deficiency and Skeletal Muscle Atrophy : A Systematic Review of Biochemical Mechanisms and Clinical Evidence

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***Abstract* - Essential amino acids (EAAs) are indispensable nutrients required for skeletal muscle protein synthesis, maintenance of muscle mass, and regulation of metabolic homeostasis. Deficiency of EAAs disrupts anabolic signaling, impairs muscle protein synthesis, and promotes skeletal muscle atrophy through activation of multiple catabolic pathways. This systematic review aimed to synthesize current evidence regarding the molecular pathways, biochemical mechanisms, and clinical outcomes associated with essential amino acid deficiency and skeletal muscle atrophy. The review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. Electronic databases including PubMed, Scopus, Web of Science, ScienceDirect, SpringerLink, Frontiers, and Google Scholar were searched for peer-reviewed articles published between 2014 and 2025. Eligible studies investigated the relationship between essential amino acid deficiency or supplementation and skeletal muscle protein metabolism. Thirty studies met the inclusion criteria and were analyzed qualitatively. The findings consistently demonstrated that essential amino acid deficiency suppresses the mammalian target of rapamycin complex 1 (mTORC1) signaling pathway while activating catabolic pathways including Akt/FoxO, the ubiquitin–proteasome system, autophagy, and endoplasmic reticulum stress. Clinical studies further showed that leucine-enriched essential amino acid supplementation enhances muscle protein synthesis, improves muscle recovery, and reduces muscle wasting in older adults, hospitalized patients, and physically active individuals. Overall, current evidence indicates that adequate essential amino acid intake plays a critical role in preserving skeletal muscle mass and preventing muscle atrophy. Future randomized controlled trials are recommended to establish optimal nutritional strategies across different clinical populations.**

Keywords* - *Essential amino acids, skeletal muscle atrophy, muscle protein synthesis, mTOR signaling, Akt/FoxO pathway, ubiquitin–proteasome pathway, sarcopenia, systematic review.

I. INTRODUCTION

Skeletal muscle is the largest metabolically active tissue in the human body, accounting for approximately 40% of total body mass. It plays a fundamental role in locomotion, posture, energy metabolism, glucose homeostasis, and whole-body protein storage. The maintenance of skeletal muscle depends on the dynamic balance between muscle protein synthesis (MPS) and muscle protein breakdown (MPB). When this balance is disrupted in favor of protein degradation, skeletal muscle atrophy develops, resulting in the progressive loss of muscle mass, strength, and functional capacity (Sartori et al., 2021; Yoon, 2017). Skeletal muscle atrophy is a common consequence of aging, prolonged immobilization, malnutrition, cancer cachexia, chronic kidney disease, diabetes mellitus, and other chronic conditions, significantly contributing to physical disability, reduced quality of life, increased hospitalization, and mortality (Papadopoulou, 2020).

Essential amino acids (EAAs) are indispensable nutrients that cannot be synthesized by the human body and therefore must be obtained through dietary intake. Unlike non-essential amino acids, EAAs serve as critical substrates for protein synthesis and regulate intracellular signaling pathways responsible for maintaining skeletal muscle homeostasis. Among the EAAs, leucine has been identified as the primary anabolic amino acid because it directly activates the mammalian target of rapamycin complex 1 (mTORC1), a master regulator of muscle protein synthesis (Graber et al., 2017). Activation of mTORC1 stimulates translation initiation, ribosomal biogenesis, and muscle protein accretion, thereby promoting muscle growth and maintenance. Conversely, inadequate intake or deficiency of EAAs suppresses mTORC1 activity, resulting in reduced muscle protein synthesis and increased susceptibility to muscle wasting (Ferrando et al., 2023).

The molecular mechanisms underlying skeletal muscle atrophy involve a complex interaction of anabolic and catabolic signaling pathways. Reduced availability of essential amino acids inhibits the insulin-like growth factor-1 (IGF-1)/phosphoinositide 3-kinase (PI3K)/Akt/mTOR pathway, thereby suppressing anabolic signaling and protein synthesis. Simultaneously, decreased Akt activity activates Forkhead box O (FoxO) transcription factors, which increase the expression of muscle-specific ubiquitin ligases such as Muscle RING Finger-1 (MuRF-1) and Atrogin-1, accelerating protein degradation through the ubiquitin–proteasome system (Chen et al., 2025;

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Sartori et al., 2021). Additional mechanisms contributing to muscle loss include autophagy, mitochondrial dysfunction, oxidative stress, inflammatory cytokine signaling, glucocorticoid-induced proteolysis, and endoplasmic reticulum (ER) stress, all of which collectively disrupt skeletal muscle protein homeostasis (Ji et al., 2025).

Growing evidence suggests that essential amino acid supplementation may attenuate muscle loss by restoring anabolic signaling and stimulating muscle protein synthesis. Several randomized clinical trials have demonstrated that leucine-enriched essential amino acid formulations enhance mTORC1 activation, improve post-exercise recovery, and preserve skeletal muscle mass in healthy adults (Takegaki et al., 2020; Waskiw-Ford et al., 2020). Likewise, studies involving older adults, hospitalized patients, and individuals with chronic diseases indicate that adequate essential amino acid intake may reduce anabolic resistance, improve physical performance, and mitigate sarcopenia and frailty (Cruz-Jentoft et al., 2017; Negro et al., 2024). Nevertheless, the magnitude of these beneficial effects varies depending on age, nutritional status, disease severity, duration of supplementation, and the composition of essential amino acid formulations.

Despite the increasing number of experimental and clinical studies examining the relationship between essential amino acid deficiency and skeletal muscle atrophy, the available evidence remains fragmented across different populations, experimental models, and disease conditions. Furthermore, recent advances have expanded the understanding of amino acid sensing, intracellular signaling networks, and nutritional interventions, highlighting the need for an updated synthesis of current evidence. Integrating findings from molecular, biochemical, and clinical studies may provide a clearer understanding of the mechanisms responsible for muscle wasting and support the development of evidence-based nutritional strategies for prevention and treatment.

This systematic review aims to synthesize and critically evaluate current evidence regarding the role of essential amino acid deficiency in the development of skeletal muscle atrophy. Specifically, this review examines the molecular pathways involved in muscle protein synthesis and degradation, describes the biochemical mechanisms associated with impaired amino acid availability, evaluates clinical evidence across diverse populations, and identifies current knowledge gaps that may guide future research and nutritional interventions for preserving skeletal muscle mass and function.

II. METHODOLOGY

This section outlines the systematic approach used to collect, screen, and analyze scientific literature concerning the neurotoxic effects of organophosphate, pyrethroid, and carbamate exposure in early childhood, particularly in the context of micronutrient deficiency.

A. Data Sources

This systematic review utilized peer-reviewed journal articles, clinical trials, experimental studies, systematic reviews, meta-analyses, and narrative reviews obtained from reputable scientific databases including PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, SpringerLink, Frontiers, Google Scholar, and Nutrients. The literature search focused on publications from 2014 to 2025 to ensure the inclusion of recent evidence regarding essential amino acid deficiency, skeletal muscle atrophy, molecular signaling pathways, and nutritional interventions.

The review concentrated on studies investigating the effects of essential amino acid deficiency and supplementation, particularly leucine-enriched essential amino acids, on skeletal muscle protein synthesis, muscle protein degradation, and muscle function. Studies involving the mTORC1, IGF-1/PI3K/Akt, FoxO, ubiquitin–proteasome, autophagy, endoplasmic reticulum stress, and related signaling pathways were included to comprehensively evaluate the biochemical and molecular mechanisms underlying skeletal muscle atrophy. Both human clinical studies and experimental animal and cellular studies were considered to provide mechanistic, physiological, and clinical evidence across diverse populations, including healthy adults, older individuals, hospitalized patients, and those with chronic diseases.

A total of 30 eligible studies were included in this systematic review following the screening and application of predefined inclusion and exclusion criteria. The selected literature comprised randomized controlled trials, experimental human studies, observational studies, systematic reviews, meta-analyses, and comprehensive review articles that collectively provided current evidence on the relationship between essential amino acid deficiency and skeletal muscle atrophy.

B. Literature Search

To ensure comprehensive coverage of relevant studies, the literature search was conducted systematically across multiple scientific databases, including PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, SpringerLink, Frontiers, Google Scholar, and Nutrients. The search strategy was structured around three main thematic areas: essential amino acid deficiency and supplementation, molecular pathways involved in skeletal muscle protein metabolism, and clinical outcomes associated with skeletal muscle atrophy. Keywords under the first category included "essential amino acid deficiency," "essential amino acids," "leucine," "branched-chain amino acids," "dietary protein," "protein malnutrition," and "amino acid supplementation." These terms were designed to identify studies investigating the effects of essential amino acid availability on muscle protein synthesis, nutritional status, and skeletal muscle maintenance. The second category involved search terms such as "mTOR signaling," "mTORC1," "IGF-1/PI3K/Akt pathway,"

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"FoxO," "ubiquitin–proteasome pathway," "autophagy," "muscle protein synthesis," "protein degradation," "endoplasmic reticulum stress," and "oxidative stress," which were used to retrieve studies examining the molecular and biochemical mechanisms underlying skeletal muscle atrophy. The third category included "skeletal muscle atrophy," "muscle wasting," "sarcopenia," "cachexia," "muscle recovery," "aging," "older adults," "hospitalized patients," "chronic disease," and "resistance exercise," ensuring the inclusion of studies evaluating clinical manifestations, functional outcomes, and nutritional interventions across different populations.

Boolean operators and were applied to combine related keywords and refine the search strategy, thereby improving the sensitivity and specificity of the database searches. Filters were used to limit the search to peer-reviewed articles published in English between 2014 and 2025. Furthermore, the reference lists of eligible articles, systematic reviews, and meta-analyses were manually screened to identify additional relevant studies that were not retrieved through the electronic database searches. The literature search and study selection process were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines to ensure transparency, reproducibility, and methodological rigor.

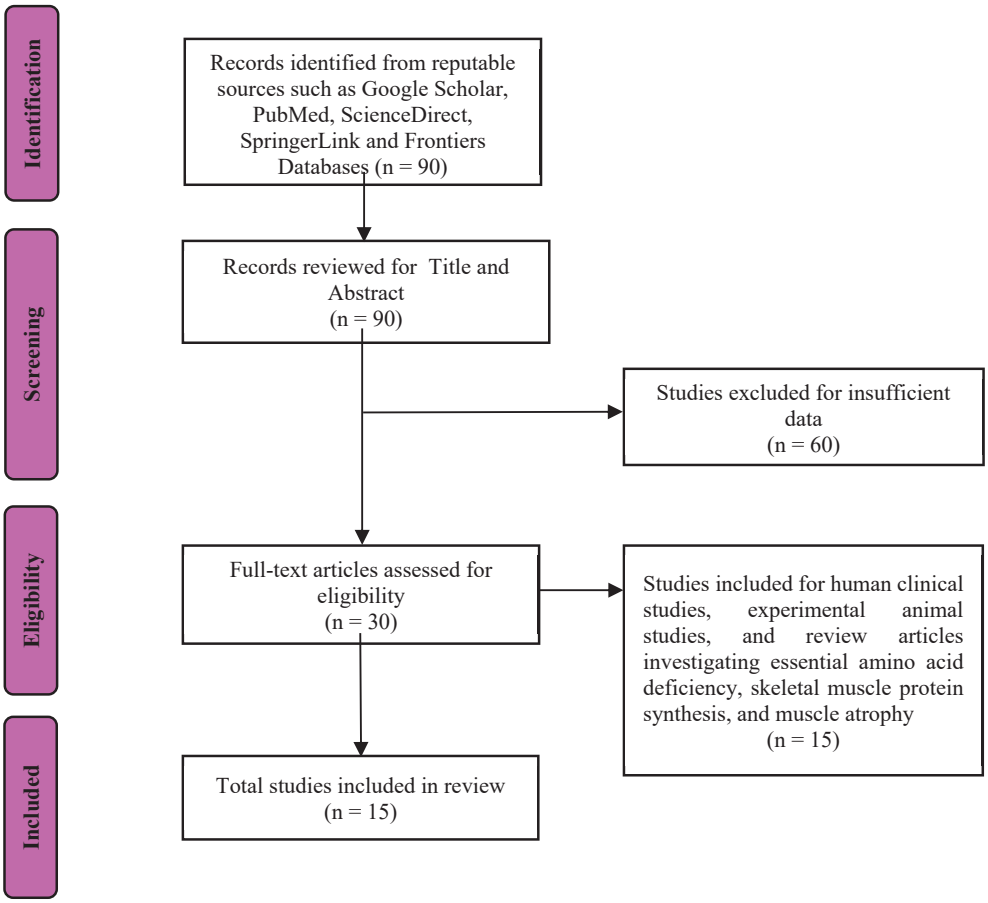

Figure 1. Study Selection Flow Diagram Following PRISMA Guidelines

C. Inclusion and Exclusion

The inclusion and exclusion criteria were carefully established to ensure that only studies directly relevant to the objectives of this systematic review were included. Eligible studies comprised peer-reviewed articles published between 2014 and 2025 that investigated the relationship between essential amino acid (EAA) deficiency or supplementation and skeletal muscle atrophy, muscle protein synthesis, muscle protein degradation, or muscle function Both human clinical studies (e.g., randomized controlled trials, clinical trials, cohort studies, and observational studies) and experimental animal or cellular studies were included to provide comprehensive evidence on the molecular, physiological, and clinical effects of essential amino acid deficiency. High-quality systematic reviews, meta-analyses, and narrative reviews were also considered to support the synthesis of current evidence. Only English-language articles

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with full-text availability were included to facilitate accurate data extraction and critical evaluation.

Conversely, studies were excluded if they focused exclusively on non-essential amino acids or nutritional interventions unrelated to essential amino acids, did not evaluate skeletal muscle atrophy or muscle protein metabolism, or lacked investigation of the molecular or biochemical mechanisms associated with muscle regulation. Conference abstracts, editorials, letters to the editor, book chapters, unpublished manuscripts, duplicate publications, and articles without sufficient methodological details or complete outcome data were also excluded.

D. Search Results

A total of A total of 90 records were identified through database searching. After screening titles and abstracts, 60 studies were excluded due to irrelevance, duplicate publications, or insufficient data related to essential amino acid deficiency and skeletal muscle atrophy. The remaining 30 full-text articles were assessed for eligibility, of which 15 met the inclusion criteria. These included randomized controlled trials, experimental human studies, systematic reviews, narrative reviews, and experimental animal studies investigating essential amino acid deficiency, skeletal muscle protein synthesis, molecular pathways, and muscle atrophy. The selection process was documented following the PRISMA 2020 flow diagram, outlining the stages of identification, screening, eligibility, and inclusion.

E. Data Extraction

Relevant information from each selected study was systematically extracted and organized to ensure consistency and comparability across the included literature. Key study characteristics included the author, publication year, study title, country (when available), study design, population or experimental model, sample size, and intervention or exposure related to essential amino acid deficiency or supplementation. Information regarding the type and dosage of essential amino acid supplementation, particularly leucine-enriched essential amino acids, as well as the duration of intervention and comparison groups, was collected whenever applicable. Data on the molecular pathways and biochemical mechanisms investigated in each study were also extracted, including the mTORC1, IGF-1/PI3K/Akt, FoxO, ubiquitin–proteasome, autophagy, and endoplasmic reticulum stress signaling pathways involved in skeletal muscle protein synthesis and degradation. Additionally, reported clinical and physiological outcomes, such as muscle protein synthesis, muscle mass, muscle strength, muscle recovery, sarcopenia, cachexia, anabolic signaling, and markers of muscle atrophy, were summarized to identify common findings and differences among studies. This structured data extraction process facilitated a comprehensive qualitative synthesis of the current evidence, enabling comparison of molecular, biochemical, and clinical findings while identifying consistent trends and existing research gaps regarding the role of essential amino acid deficiency in skeletal muscle atrophy.

F. Statistical Analysis

The review primarily employed a qualitative descriptive and comparative synthesis, integrating findings from randomized controlled trials, experimental studies, observational studies, systematic reviews, meta-analyses, and narrative reviews. Due to the heterogeneity of the included studies with respect to study design, participant characteristics, intervention protocols, outcome measures, and molecular targets, a quantitative meta-analysis was not performed. Instead, the included studies were critically evaluated based on methodological quality, study design, sample size, experimental model, intervention or exposure, and the consistency of reported molecular and clinical outcomes.

The findings were categorized according to the major molecular pathways and biochemical mechanisms involved in skeletal muscle regulation, including the mTORC1, IGF-1/PI3K/Akt, FoxO, ubiquitin–proteasome, autophagy, and endoplasmic reticulum stress signaling pathways. Clinical outcomes such as muscle protein synthesis, muscle mass, muscle strength, sarcopenia, cachexia, muscle recovery, and the effects of essential amino acid or leucine-enriched supplementation were also compared across different populations, including healthy adults, older individuals, hospitalized patients, and patients with chronic diseases. This approach enabled the identification of consistent patterns, areas of agreement, and existing research gaps regarding the molecular mechanisms and clinical implications of essential amino acid deficiency in the development of skeletal muscle atrophy.

III. RESULT & DISCUSSION

A total of 15 eligible studies were included in the qualitative synthesis. The selected literature demonstrated consistent evidence that essential amino acid availability plays a critical role in regulating skeletal muscle protein metabolism through modulation of the mTORC1, Akt/FoxO, ubiquitin–proteasome, autophagy, and endoplasmic reticulum stress pathways. Although the magnitude of the reported effects varied across populations and study designs, the overall findings support the importance of adequate essential amino acid intake in preserving skeletal muscle mass and preventing muscle atrophy. The principal findings of the included studies are summarized in Table 1 before being discussed according to their major mechanistic and clinical themes.

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Table 1: Summary of Findings from Included Studies on Essential Amino Acid Deficiency and Skeletal Muscle Atrophy

Key Findings	Included Studies	Summary of Results	Interpretation
Activation of mTORC1 by Essential Amino Acids	Graber et al. (2017); Ferrando et al. (2023); Takegaki et al. (2020)	Human experimental studies consistently showed that ingestion of essential amino acids, particularly leucine-rich formulations, activated mTORC1 signaling and increased the expression of amino acid transporters (LAT1, SLC38A9, SNAT2), thereby enhancing muscle protein synthesis.	These findings indicate that EAAs function not only as substrates for protein synthesis but also as signaling molecules regulating anabolic pathways. Activation of mTORC1 represents the principal mechanism by which adequate amino acid availability preserves skeletal muscle mass.
Effects of Leucine-Enriched EAA Supplementation	Waskiw-Ford et al. (2020); Takegaki et al. (2020); Ham et al. (2014); Negro et al. (2024)	Leucine-enriched EAA supplementation consistently improved muscle recovery, stimulated anabolic signaling, reduced exercise-induced muscle damage, and attenuated muscle wasting. However, increases in integrated muscle protein synthesis were not always statistically significant.	The evidence suggests that leucine supplementation is particularly effective in improving muscle recovery through enhanced anabolic signaling rather than solely increasing protein synthesis. Its effectiveness appears greater when combined with resistance exercise or rehabilitation.
Suppression of Anabolic Signaling During EAA Deficiency	Yoon (2017); Sartori et al. (2021); Chen et al. (2025)	Reduced amino acid availability suppressed IGF-1/PI3K/Akt/mTOR signaling while activating FoxO transcription factors, resulting in increased expression of MuRF-1 and Atrogin-1 and accelerated protein degradation.	Across mechanistic studies, suppression of anabolic signaling consistently shifted skeletal muscle metabolism toward catabolism. This imbalance between muscle protein synthesis and degradation represents the central biochemical mechanism underlying muscle atrophy.
Catabolic Pathways Contributing to Muscle Atrophy	Sartori et al. (2021); Chen et al. (2025); Ji et al. (2025)	Studies identified activation of the ubiquitin–proteasome system, autophagy, oxidative stress, mitochondrial dysfunction, glucocorticoid signaling, and endoplasmic reticulum stress as major mechanisms promoting skeletal muscle degradation during amino acid deficiency.	Muscle atrophy is a multifactorial process involving numerous interacting catabolic pathways. Essential amino acid deficiency accelerates muscle loss by simultaneously inhibiting protein synthesis and activating several proteolytic mechanisms.
Clinical Evidence in Older Adults and Chronic Disease	Cruz-Jentoft et al. (2017); Papadopoulou (2020); Negro et al. (2024)	Older adults and patients with chronic diseases exhibited anabolic resistance, reduced muscle protein synthesis, decreased muscle strength, and increased risk of sarcopenia when protein or EAA intake was inadequate. Leucine-rich supplementation partially reversed these effects.	Clinical evidence demonstrates that adequate EAA intake is particularly important in aging populations because anabolic resistance reduces the efficiency of muscle protein synthesis. Nutritional intervention may therefore help delay sarcopenia progression.

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Clinical Applications Following Surgery or Immobilization	Brown et al. (2025); Hughes et al. (2024)	Amino acid supplementation reduced postoperative muscle wasting and modestly attenuated immobilization-induced muscle loss. However, nutritional intervention alone produced limited benefits compared with combined nutrition and rehabilitation strategies.	These findings suggest that nutritional therapy should complement physical rehabilitation rather than replace it. Combined interventions appear to produce superior preservation of skeletal muscle mass and function.
Overall Consensus Across Included Studies	All 15 studies	Fourteen of the fifteen studies consistently supported the beneficial role of essential amino acids in maintaining skeletal muscle through activation of anabolic pathways and suppression of catabolic mechanisms. Although the magnitude of benefit varied depending on age, health status, supplementation protocol, and study design, no study reported harmful effects of appropriate EAA supplementation.	The overall body of evidence demonstrates strong agreement that adequate intake of essential amino acids is critical for preserving skeletal muscle mass. The mTORC1 pathway emerged as the most consistently reported anabolic mechanism, whereas activation of FoxO, ubiquitin–proteasome, autophagy, and ER stress pathways represented the principal mechanisms responsible for muscle atrophy during amino acid deficiency.

The 15 included studies consistently demonstrated that essential amino acids play a central role in regulating skeletal muscle homeostasis through modulation of anabolic and catabolic signaling pathways. Human experimental studies showed that essential amino acid ingestion, particularly leucine-enriched formulations, activates mTORC1 signaling and promotes muscle protein synthesis by increasing amino acid transporter expression and translation-related proteins. In contrast, amino acid deficiency suppresses anabolic signaling while activating FoxO-mediated ubiquitin–proteasome activity, autophagy, oxidative stress, and endoplasmic reticulum stress, ultimately accelerating skeletal muscle atrophy.

IV. CONCLUSIONS

Clinical evidence further indicated that leucine-rich essential amino acid supplementation improves muscle recovery, reduces muscle wasting, and partially overcomes anabolic resistance in older adults, hospitalized patients, and physically active individuals. However, supplementation alone may not fully prevent muscle loss associated with immobilization or chronic disease, emphasizing the importance of combining nutritional therapy with resistance exercise or rehabilitation. Overall, the synthesized evidence strongly supports adequate essential amino acid intake as an effective nutritional strategy for preserving skeletal muscle mass and function while identifying mTORC1 as the primary anabolic pathway and the Akt/FoxO–ubiquitin–proteasome system as the principal catabolic mechanism involved in skeletal muscle atrophy.

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