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Review

# Effects of pharmacological interventions on muscle protein synthesis and breakdown in recovery from burns

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ABSTRACT

*Objective:* The pathophysiological response to burn injury disturbs the balance between skeletal muscle protein synthesis and breakdown, resulting in severe muscle wasting. Muscle loss after burn injury is related to increased mortality and morbidity. Consequently, mitigation of this catabolic response has become a focus in the management of these patients. The aim of this review is to discuss the literature pertaining to pharmacological interventions aimed at attenuating skeletal muscle catabolism in severely burned patients.

Data selection: Review of the literature related to skeletal muscle protein metabolism following burn injury was conducted. Emphasis was on studies utilizing stable isotope tracer kinetics to assess the impact of pharmacological interventions on muscle protein metabolism in severely burned patients.

*Conclusion:* Data support the efficacy of testosterone, oxandrolone, human recombinant growth hormone, insulin, metformin, and propranolol in improving skeletal muscle protein net balance in patients with severe burns. The mechanisms underlying the improvement of protein net balance differ between types and dosages of drugs, but their main effect is on protein synthesis. Finally, the majority of studies have been conducted during the acute hypermetabolic phase of the injury. Except for oxandrolone, the effects of drugs on muscle protein kinetics following discharge from the hospital are largely unknown.



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*Abbreviations:* TBSA, Total body surface area; LBM, Lean body mass; REE, Resting energy expenditure; PSE, Protein synthesis efficiency; rhGH, Recombinant human growth hormone.

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## Contents



## 1. Introduction

Severe thermal injury, defined as wounds compromising more than 40% of the patient's total body surface area (TBSA), is followed by a severe hypermetabolic response [1] and dramatic elevations in the protein synthesis and breakdown rates [2]. The efflux of amino acids from skeletal muscle in response to burn injury is thought to supply substrate for vital processes such as wound healing, immune function and hepatic protein synthesis [3,4]. Although necessary for recovery, this pathophysiologic response leads to an extensive loss of skeletal muscle protein that is not easily reversed by aggressive nutritional support alone [5].

Prolonged catabolism of lean body mass (LBM) has been associated with detrimental outcomes such as muscle weakness, immune-suppression, impaired wound healing [6], severe growth arrest [7], delayed recovery and rehabilitation, and even decreased survival rates [8]. Thus, amelioration of skeletal muscle loss to improve strength and function and to decrease physical and functional impairment is of major importance for enhancing the recovery process and improving survival rates in severe burn victims.

The purpose of this review is to discuss the current data pertaining to the effects of pharmacological interventions on muscle protein synthesis, breakdown and net balance (synthesis minus breakdown) following a major thermal injury.

## 2. Acute burn-induced changes in skeletal muscle protein kinetics

In otherwise healthy humans, muscle mass is maintained through a dynamic balance between protein accretion and protein degradation [9]. To evaluate the impact of the burn injury on muscle protein metabolism, Biolo et al. [5] determined protein synthesis and breakdown rates and also transmembrane transport of amino acids in 18 normal volunteers and 19 acutely burned adult patients. In the post-absorptive state, the absolute rates of muscle protein synthesis and breakdown were elevated in the burn group by 50% and 83%, respectively. Thus, the marked increase in muscle protein breakdown rate was not matched by a synthetic response of the same magnitude, leading to a significantly more negative net protein balance in the burn group.

Further, the rate at which amino acids were delivered to the leg was 2–3 times greater in the burn cohort due to a two-fold elevation in the rate of leg blood flow. However, absolute inward amino acid transport into the muscle was not significantly different in patients compared to controls. In fact, after normalizing for the delivery rate to the leg, the capacity of the transport systems was found to be attenuated by 50–63% in the burn group. On the other hand, the efflux of amino acids being traced was ~50% greater in the burn patients compared to the control subjects.

Under normal circumstances, amino acids in the free intracellular pool can derive either from the breakdown of proteins or from the inward transport of amino acids. In the aforementioned study, the rate of intracellular appearance of essential amino acids increased following burn trauma. For example, the intracellular concentration of leucine was 1.7-fold greater in burn patients than controls (358 vs. 206 nmol/ml). Interestingly, this occurred despite an impaired amino acid transport system, suggesting that amino acids in the intracellular free pool may derive primarily from the breakdown of muscle protein (Fig. 1).

The profoundly elevated muscle protein breakdown would saturate the intracellular free pool of amino acids leading to a concurrent elevation in the rate of muscle protein synthesis [5], since the availability of free amino acids is an important limiting step in this process [10]. However, this elevation in protein synthesis is not adequate to compensate for the increased rate of protein breakdown, which over time results in muscle wasting.