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The recovery hormone: oxandrolone as a strategic ally in intensive care.

The recovery hormone: oxandrolone as an adjuvant strategy in intensive care

The restorative hormone: oxandrolone as a strategic ally in intensive care

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Abstract: Severe burns constitute a complex clinical condition and represent a significant cause of morbidity and mortality among hospitalized patients. Extensive thermal injury triggers a systemic pathophysiological response characterized by persistent hypermetabolism, exacerbated inflammation, and intense protein catabolism, factors that contribute to significant muscle mass loss, delayed healing, and increased risk of infectious complications. Different therapeutic strategies have been investigated to reduce the effects of metabolic catabolism in burn patients. Among them, oxandrolone stands out.

which has the potential to stimulate protein synthesis and preserve lean mass. The objective of this study was to analyze the effects of oxandrolone use on the metabolic and functional recovery of adult patients with severe burns admitted to intensive care units. This is an integrative literature review, conducted through searches in the PubMed, LILACS, SciELO, and BVS databases, including articles published between 2000 and 2025 that address the application of oxandrolone in patients with severe burns, its effects on the hypermetabolic state, protein catabolism, and the optimization of clinical outcomes. The results indicate that oxandrolone administration is associated with improved nitrogen balance, reduced protein catabolism, and preservation of muscle mass. Studies point to benefits related to the healing process and functional recovery. The review showed that oxandrolone may represent an adjuvant therapeutic strategy in the metabolic management of patients with severe burns, especially when associated with adequate nutritional support and rigorous clinical monitoring.

Keywords: severe burns, oxandrolone, hypermetabolism, intensive care.
Protein catabolism.

Abstract: Severe burns represent a complex clinical condition and are an important cause of morbidity and mortality among hospitalized patients. Extensive thermal injury triggers a systemic pathophysiological response characterized by persistent hypermetabolism, exacerbated inflammation, and intense protein catabolism, all of which contribute to significant loss of muscle mass, delayed wound healing, and an increased risk of infectious complications. Different therapeutic strategies have been investigated to reduce the effects of metabolic catabolism in burn patients. Among these, oxandrolone has emerged as a potential agent that stimulates protein synthesis and preserves lean body mass. This study aimed to analyze the effects of oxandrolone use on the metabolic and functional recovery of adult patients with severe burns admitted to intensive care units. This is an integrative literature review conducted through searches in the PubMed/MEDLINE, LILACS, SciELO, and Virtual Health Library (VHL) databases, including studies published between 2000 and 2025 that address the use of oxandrolone in patients with severe burns, its effects on the hypermetabolic state, protein catabolism, and clinical outcomes. The

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findings indicate that oxandrolone administration is associated with improved nitrogen balance, reduced protein catabolism, and preservation of muscle mass. The studies also suggest benefits related to wound healing and functional recovery. The review demonstrated that oxandrolone may represent an adjuvant therapeutic strategy in the metabolic management of patients with severe burns, especially when combined with adequate nutritional support and careful clinical monitoring.
Keywords: severe burns. oxandrolone. hypermetabolism. intensive care. protein catabolism.

1. Introduction

Severe burns represent a significant public health problem at the global level.
globally, they are responsible for high morbidity and mortality rates and high healthcare costs. It is estimated
that approximately 11 million people require medical attention for burns
each year worldwide, with a greater impact on low- and middle-income countries, where the incidence and
Associated complications tend to be more pronounced (WORLD HEALTH ORGANIZATION,
2023).

In the most severe cases, involving a large area of the body burned,
Patients require prolonged hospitalization and management in intensive care units.
due to the complexity of the systemic changes triggered by thermal injury, in which the
The systemic pathophysiological response involves metabolic, hormonal, and immunological alterations.
deep (JESCHKE et al., 2020).

Following thermal trauma, intense activation of the systemic inflammatory response occurs.
accompanied by the release of pro-inflammatory cytokines, by increased secretion of
catecholamines and the activation of the hypothalamic-pituitary-adrenal axis. These mechanisms result in
a persistent hypermetabolic state characterized by a significant increase in energy expenditure
basal, peripheral insulin resistance and intensification of protein catabolism (JESCHKE et al.,
2020; WILLIAMS; HERNDON; JESCHKE, 2020).

The hypermetabolism associated with severe burns can persist for weeks or even longer.
months after the initial trauma, constituting one of the main causes of clinical deterioration in these cases.
patients. The prolonged metabolic state promotes accelerated protein degradation.
muscular, leading to progressive loss of lean body mass and impaired function.
Muscle loss. Studies show that patients with extensive burns may experience muscle loss.
Significant muscle mass gain in the first few weeks after injury, a factor associated with increased...
length of hospital stay, delays in rehabilitation, and a higher risk of infectious complications.
(PORTER et al., 2021; SHANKAR; FINNERTY; HERNDON, 2021).

In this way, the loss of integrity of the skin barrier favors bacterial colonization.
and significantly increases the risk of systemic infections, remaining among the leading causes.

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causes of morbidity and mortality in patients with severe burns. The association between Persistent systemic inflammation, relative immunosuppression, and intense protein catabolism create a A complex clinical scenario that demands therapeutic strategies capable of reducing the deleterious effects. of hypermetabolism (GREENHALGH, 2022).

In this context, different therapeutic approaches have been investigated with the aim of modulate the metabolic response after severe burns, including intensive nutritional support, Pharmacological interventions and the use of anabolic agents. Among these agents, the following stand out: oxandrolone, a synthetic anabolic steroid derived from dihydrotestosterone, which has high anabolic activity and low androgenic activity are characteristics that favor its clinical use in critically ill patients (RING et al., 2020; KRAFT; HERNDON; FINNERTY, 2021).

Oxandrolone acts primarily by activating androgen receptors in muscle tissue, promoting increased protein synthesis, improved nitrogen balance and... Reduction of muscle catabolism. Recent evidence indicates that its administration in patients with extensive burns it can contribute to the preservation of lean body mass, the acceleration of the healing process and improvement of functional recovery during the phase of rehabilitation (ZHANG et al., 2022; ZHOU et al., 2023).

Therefore, understanding the therapeutic effects of oxandrolone in the context of alterations Understanding metabolic issues resulting from severe burns becomes crucial for improving strategies. treatment of patients admitted to intensive care units. The present study aims to The objective is to analyze the effects of oxandrolone use on the metabolic and functional recovery of Adult patients with severe burns admitted to intensive care units.

2. Theoretical Framework

2.1 Pathophysiological and metabolic changes and inflammatory response in patients with severe burns

Severe burns trigger a complex cascade of pathophysiological responses. which involve metabolic, immunological, and hormonal changes. These changes occur as The body's adaptive mechanism in response to thermal trauma; however, when exacerbated and Prolonged cases can contribute to significant clinical deterioration and an increase in... morbidity and mortality, since the systemic response affects multiple organs and systems, and are considered one of the main causes of complications during hospital admission (JESCHKE et al., 2020; STANOJCIC et al., 2020).

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Extensive thermal injury triggers immediate activation of the innate immune system, with the release of inflammatory mediators, such as interleukins (IL-1, IL-6), tumor necrosis factor alpha (TNF-ÿ) and prostaglandins. These mediators play a fundamental role in amplification of the systemic inflammatory response, contributing to increased permeability vascular, the recruitment of inflammatory cells, and the activation of metabolic pathways associated with physiological stress (WILLIAMS; HERNDON; JESCHKE, 2020).

The inflammatory response triggered by severe burns can develop into a syndrome. systemic inflammatory response syndrome (SIRS), a condition frequently observed in patients admitted to intensive care units and associated with multiple organ dysfunction and increased susceptibility to secondary infections (JESCHKE et al., 2020).

One of the striking characteristics of the pathophysiology of severe burns is... development of a persistent hypermetabolic state, which causes continuous release of catabolic hormones, such as catecholamines, cortisol, and glucagon, promoting an increase in basal energy metabolism and increased mobilization of energy substrates, leading to development of insulin resistance (PORTER et al., 2021; SHANKAR; FINNERTY; HERNDON, 2021).

Another aspect of the pathophysiology of severe burns is intense protein catabolism. Accelerated degradation of muscle proteins occurs as a consequence of the need for The body's ability to mobilize amino acids for acute-phase protein synthesis, the production of Inflammatory mediators and tissue repair (PORTER et al., 2021).

Resulting in significant loss of lean body mass in the first few weeks after the Thermal trauma, a factor associated with increased mechanical ventilation time, and prolonged from hospital admissions to higher mortality (KRAFT; HERNDON; FINNERTY, 2021).

2.2 Therapeutic strategies for modulating hypermetabolism

Given the complexity of the metabolic changes associated with severe burns, Different therapeutic strategies have been proposed with the aim of reducing the effects of hypermetabolism and protein catabolism, preserving lean body mass and improving clinical outcomes for these patients. Among these strategies, nutritional support stands out. intensive pharmacological interventions aimed at neuroendocrine modulation and programs structured early physical rehabilitation, considered fundamental components of management multidisciplinary approach to the critically ill burn patient (PORTER et al., 2021; WILLIAMS; HERNDON; JESCHKE, 2020).

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Early enteral nutrition is one of the main therapeutic interventions for to mitigate the post-burn hypercatabolic response, and should preferably be initiated in The first 6 to 12 hours after thermal trauma. This strategy contributes to maintaining the Intestinal mucosal integrity, reduction of bacterial translocation, modulation of the response systemic inflammation and the adequate supply of necessary energy and protein substrates to the synthesis of structural proteins and tissue repair (PORTER et al., 2021). (SHANKAR; FINNERTY; HERNDON, 2021).

Among the pharmacological interventions used in modulating the hypermetabolic response, Beta-adrenergic blockers stand out, particularly propranolol, which acts by reducing The effects of sustained sympathetic hyperactivity observed after extensive burns. Propranolol administration is associated with a reduction in basal energy expenditure and a decrease in... peripheral lipolysis and preservation of lean body mass, contributing to the improvement of metabolic efficiency and for the reduction of the systemic catabolic state (PORTER et al., 2021).

Another relevant strategy involves the use of intensive insulin therapy, which presents important metabolic effects, such as the reduction of persistent hyperglycemia, the improvement of Peripheral glucose uptake and stimulation of muscle protein synthesis. Insulin also exerts a modulating role in the inflammatory response and may contribute to improved healing and to reduce the incidence of infectious complications in patients with extensive burns. (WILLIAMS; HERNDON; JESCHKE, 2020).

Furthermore, anabolic agents have been extensively investigated as a strategy. A therapeutic approach to minimize protein catabolism associated with a prolonged hypermetabolic state. Among these agents, growth hormone, testosterone, and steroids stand out. synthetic anabolics, particularly oxandrolone. (RING et al., 2020; KRAFT; HERNDON; FINNERTY, 2021).

Additionally, structured early physical rehabilitation programs have demonstrated... plays a relevant role in modulating muscle hypercatabolism and in functional recovery of Burn patients, contributing to improved peripheral muscle strength and reduced recovery time. mechanical ventilation and a decrease in the length of hospital stay. The association between Adequate nutritional support, pharmacological interventions, and early mobilization represent currently one of the most effective approaches for attenuating the hypermetabolic response persistent observed after severe burns (JESCHKE et al., 2020).

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2.2.1 Oxandrolone as anabolic therapy in burn patients

Oxandrolone is a synthetic anabolic steroid derived from dihydrotestosterone. characterized by high anabolic activity and low androgenic activity, properties that They favor its therapeutic use in clinical conditions associated with accelerated bone mass loss. muscular, as occurs in patients with extensive burns. Unlike other anabolic steroids, exhibit a lower potential for virilizing effects and less interference with The hypothalamic-pituitary-gonadal axis contributes to a more favorable safety profile. when used under appropriate clinical monitoring (RING et al., 2020; KRAFT; HERNDON; FINNERTY, 2021).

Its mechanism of action is primarily related to the activation of receptors. Intracellular androgens in skeletal muscle tissue, promoting gene transcription of structural proteins and the activation of anabolic pathways dependent on the mTOR complex (mechanistic (target of rapamycin), with a consequent increase in protein synthesis and reduction in muscle proteolysis. mediated by the ubiquitin-proteasome system. This effect contributes directly to the improvement of nitrogen balance and for the preservation of lean body mass in patients undergoing intense metabolic stress, such as occurs after severe burns (ZHANG et al., 2022; ZHOU et al., 2023).

In the context of extensive burns, oxandrolone acts as a modulator of the state. Persistent hypercatabolic state, triggered by sympathetic hyperactivity and sustained release. of catecholamines and cortisol. Administration of the drug is associated with reduced degradation. muscle protein, to improve metabolic efficiency in amino acid utilization and to attenuation of the loss of lean mass observed during the prolonged hypermetabolic phase (PORTER et al., 2021; SHANKAR; FINNERTY; HERNDON, 2021).

Patients with severe burns often present with nitrogen imbalance. Persistent negative result, a condition directly related to the intensification of muscle proteolysis and to increased hepatic synthesis of acute-phase proteins. In this scenario, the use of agents Anabolic steroids, such as oxandrolone, contribute to the partial reversal of this catabolic state. promoting the maintenance of skeletal muscle mass and improving functional recovery (KRAFT; HERNDON; FINNERTY, 2021).

In addition to its effects on muscle protein metabolism, oxandrolone exerts an impact Relevant in the healing process of skin lesions. Studies demonstrate that the drug It stimulates fibroblast activity, increases the deposition of collagen types I and III, and promotes... reorganization of the extracellular matrix, contributing to the acceleration of wound closure and

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to reduce the time required for adequate epithelialization of burned areas (ZHOU et al., 2023).

Despite the described benefits, the use of oxandrolone requires clinical monitoring. rigorous, especially regarding liver function and serum lipid profile. Among the adverse effects The most frequently reported side effects include transient elevation of liver enzymes and fluid retention. mild water retention and subtle changes in lipid metabolism. However, systematic reviews Recent studies demonstrate that the drug has an acceptable safety profile when administered. in appropriate therapeutic doses and for controlled periods in patients with severe burns. (RING et al., 2020; ZHANG et al., 2022).

3. Materials and Methods

This study is characterized as an integrative literature review, conducted with based on the methodological recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), with the aim of gathering and analyzing scientific evidence on the use of Oxandrolone in the metabolic management of adult patients with severe burns hospitalized in intensive care units.

This review was conducted based on the following guiding question: what are the effects of oxandrolone on modulating the hypermetabolic response and metabolic recovery and functional assessment of adult patients with severe burns admitted to intensive care units Intensive?

The bibliographic search was conducted in the Medical Literature Analysis and databases. Retrieval System Online (PubMed/MEDLINE), Scientific Electronic Library Online (SciELO), Latin American and Caribbean Literature in Health Sciences (LILACS) and Virtual Library in Health (BVS).

For the search strategy, controlled and uncontrolled descriptors were used in Portuguese and English, combined using the Boolean operators AND and OR, as follows strategy: (“oxandrolone”) AND (“burns” OR “severe burns”) AND (“hypermetabolism” OR “metabolic response”) AND (“intensive care” OR “critical care”), the equivalent strategy in The Portuguese version was: (“oxandrolone”) AND (“severe burns”) AND (“hypermetabolism”) AND (“intensive care”)

Studies published between 2020 and 2025 and available in full in Portuguese were included. English or Spanish, that addressed the use of oxandrolone in patients with severe burns,

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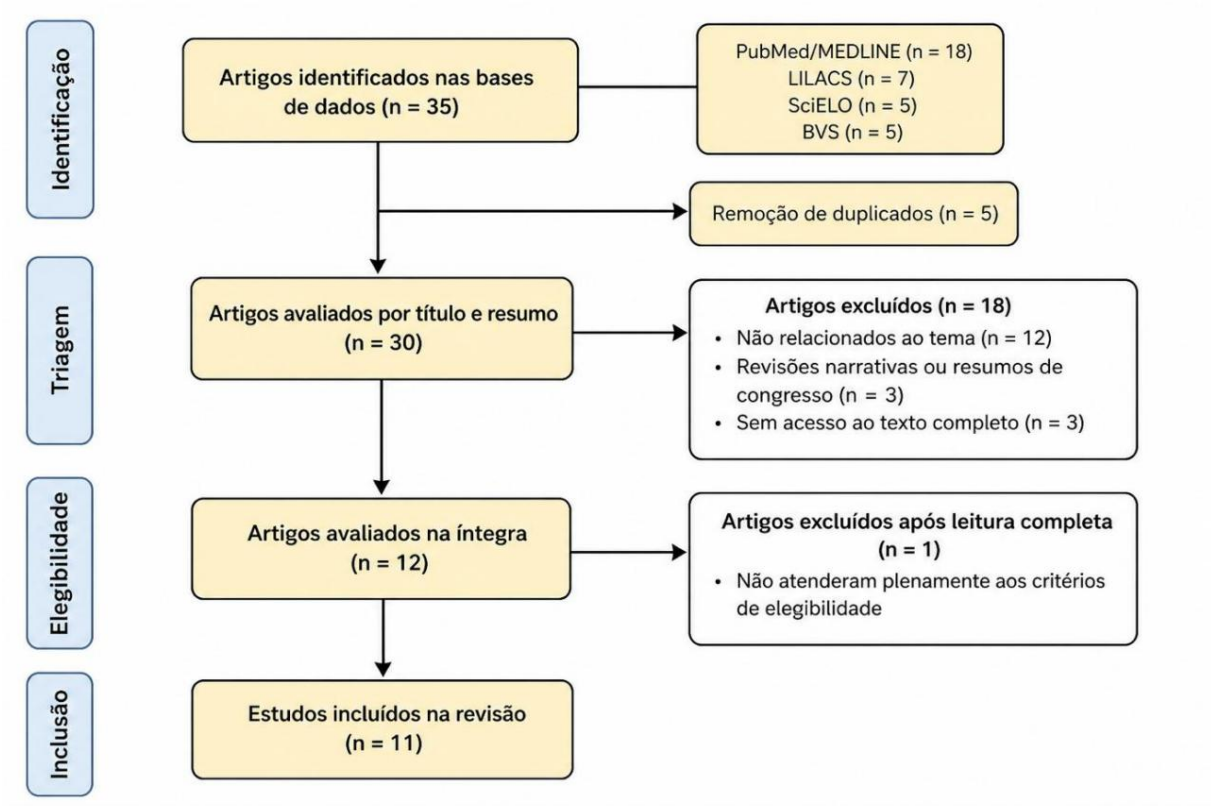
as well as its effects on hypermetabolism, protein catabolism, and mass preservation.
muscular and clinical outcomes related to functional recovery.

Duplicate articles across the consulted databases and studies without a direct relationship were excluded.
with the research topic, narrative reviews, letters to the editor, abstracts of scientific events,
dissertations, monographs and publications without access to the full text.

As shown in Figure 1, 35 studies were initially identified in the databases.
selected. After removing 5 duplicate articles, 30 publications remained for initial analysis.
Next, the titles and abstracts were read, and 18 studies were excluded because they did not meet the criteria.
meet the previously established eligibility criteria. At the end of the screening process,
Eleven articles were deemed eligible and included in this integrative review. These studies
They were analyzed qualitatively with respect to metabolic, functional, and clinical outcomes.
associated with the use of oxandrolone in patients with severe burns admitted to units
intensive care.

The process of identifying, screening, determining eligibility, and including studies is underway.
represented in the PRISMA flowchart shown in Figure 1.

Figure 1. Flowchart for selecting studies included in the integrative review, according to the
PRISMA recommendations.



Source: Authors, 2026.

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4. Results and Discussion

In total, 11 articles were found suitable for analysis in this review. Highlights-
These studies were selected and organized by author, year of publication, and country of origin.
implementation, methodological design, study objectives, methods employed and main
results regarding the metabolic, nutritional, and functional effects of the drug in individuals
patients with extensive burns in intensive care units, as presented in
Table 1.

Overall, the findings show consistency regarding the presence of a response.
Persistent hypermetabolic state following thermal trauma, characterized by increased energy expenditure.
basal metabolic rate, peripheral insulin resistance, increased muscle proteolysis, and hormonal changes.
prolonged, factors directly related to the worsening of the clinical prognosis (PORTER et
al., 2021; SHANKAR; FINNERTY; HERNDON, 2021).

Table 1. Characterization of the productions included in the review, according to: article, author, year, country, Study design, objective, methodology, and main results.

Article	Author/Year	Country	Outline	Objective	Key results
1	Ring et al., 2020	USA	Systematic Review	Evaluate the effectiveness of oxandrolone.	Increased lean mass, decreased catabolism.
2	Zhang et al., 2022	China	Meta-analysis	Assess body composition	nitrogen balance ÿ
3	Zhou et al., 2023	China	Systematic Review	Assess healing	collagen deposition
4	Jeschke et al., 2020	US	Structured Review	Metabolic response	Persistent hypermetabolism
5	Porter et al., 2021	US	Translational Review	Hypercatabolic response	ÿ basal energy expenditure
6	Shankar et al., 2021	US	Clinical Review	Assess hypermetabolism	Insulin resistance
7	Williams et al., 2020	US	Clinical Review	Metabolic response	ÿ catecholamines
8	Kraft et al., 2021	USA	Therapeutic Review	Assess anabolic therapy	Muscle preservation
9	Greenhalgh, 2022	US	Clinical Review	Burn in infections	ÿ risk of infection
10	Sidossis et al., 2021	USA	Clinical trial	Muscle metabolism ÿ protein synthesis	
11	Finnerty et al., 2021	US	Endocrine Review	Hormonal response	cortisol persistent ÿ

Maintaining this hypercatabolic state is strongly associated with hyperactivity.
sustained neuroendocrine response. In this sense, Williams, Herndon, and Jeschke (2020) demonstrated that

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The persistent elevation of catecholamines plays a central role in amplifying metabolism.
Basal energy expenditure and the continuous mobilization of protein and lipid substrates. These findings are reinforced by Finnerty, Herndon and Jeschke (2021), who showed a prolonged increase in cortisol secretion following extensive burns, which contributed to the intensification of proteolysis. muscular function and the maintenance of a negative nitrogen balance. Together, these mechanisms They help explain the difficulty in spontaneously reversing the catabolic state in these patients.

In addition to hormonal changes, peripheral insulin resistance, described by Shankar, Finnerty and Herndon (2021) argue that this constitutes a determining element in the perpetuation of post-burn hypermetabolism, since it compromises the efficient use of glucose by the peripheral tissues and promotes the degradation of muscle proteins as an alternative source of energy. In line with these findings, Sidossis et al. (2021) demonstrated a reduction significant improvement in the efficiency of muscle protein synthesis in patients with severe burns, reinforcing the relationship between systemic metabolic dysfunction and accelerated loss of body mass. skinny.

Another relevant aspect identified in the analyzed studies refers to the impact of these. metabolic changes in the clinical evolution of patients. Greenhalgh (2022) highlighted that the persistence of systemic inflammation, associated with loss of skin barrier integrity, It promotes the development of secondary infections and progressive organ dysfunction. constituting an important determinant of morbidity and mortality in this population group. These The findings broaden the understanding that hypermetabolism is not just an adaptive response. not only due to trauma, but also a central component of the clinical severity of extensive burns.

In the context of therapeutic interventions, convergence was observed between the studies. Regarding the role of anabolic agents in modulating the catabolic response. Kraft, Herndon and Finnerty (2021) demonstrated that the use of oxandrolone is associated with the preservation of mass. Lean body mass and improved functional recovery, especially when integrated with strategies Early nutritional therapy and intensive metabolic support. Similar results were described by Ring et al. (2020), who demonstrated a significant reduction in muscle loss and improvement in Functional capacity during the hospital rehabilitation period.

In addition, the meta-analysis conducted by Zhang et al. (2022) demonstrated that Oxandrolone administration promotes consistent improvement in nitrogen balance and increased... Lean body mass in patients with extensive burns, suggesting an anabolic effect. sustained even in scenarios of high metabolic demand. These findings reinforce the hypothesis. early pharmacological intervention may contribute to the attenuation of muscle proteolysis. and for optimizing functional recovery during the critical phase of hospitalization.

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In addition to the effects on protein metabolism, Zhou et al. (2023) observed an impact
The positive effect of oxandrolone on the tissue healing process, with increased deposition of
collagen and reorganization of the extracellular matrix, suggesting the benefits of the drug.
They go beyond muscle preservation and also include improved skin regeneration.
This aspect broadens the therapeutic potential of oxandrolone within the context of an approach.
multidimensional of the severely burned patient.

Additionally, Porter et al. (2021) highlighted that pharmacological interventions
Techniques aimed at modulating the hypermetabolic response are more effective when combined with...
Appropriate nutritional strategies and early mobilization demonstrate that the isolated use of
Anabolic agents have a limited impact when not integrated into therapeutic protocols.
multidisciplinary. This understanding is corroborated by Jeschke et al. (2020), who highlighted the
importance of the combined approach of high-protein nutritional support, control
neuroendocrine hypermetabolism and structured physical rehabilitation programs for
to enhance the therapeutic effects of oxandrolone.

Despite the consistency of the results related to the preservation of lean body mass,
Due to improvements in nitrogen balance and an acceleration of the healing process, it is observed that...
There are discrepancies in the literature regarding the impact of oxandrolone on broader clinical outcomes.
such as the reduction in mortality and total length of hospital stay. Zhang et al. (2022)
They point out that this limitation may be related to methodological heterogeneity among the studies.
available, including differences in administered doses, time to start therapy, and in
clinical characteristics of the populations evaluated. Similarly, Ring et al. (2020) highlight
the need for controlled clinical studies with greater methodological standardization for
definitive consolidation of oxandrolone's role in these outcomes.

Thus, the integrated analysis of the studies shows that oxandrolone has a therapeutic effect.
relevant in modulating the hypermetabolic state associated with severe burns, especially
with regard to preserving lean body mass, improving muscle protein synthesis, and
acceleration of the healing process, although gaps remain regarding its impact on
larger-scale clinical outcomes, indicating the need for future investigations with
more robust methodological designs.

Final Considerations

The evidence analyzed in this integrative review demonstrates that oxandrolone
plays a relevant therapeutic role in modulating metabolic changes associated with

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severe burns, especially with regard to mitigating the hypercatabolic state.
persistent, leading to improved nitrogen balance and preservation of lean body mass during the
length of stay in intensive care units.

The included studies show that the benefits of the drug are directly related to...
related to its anabolic action on skeletal muscle tissue, to improving efficiency
metabolic in the utilization of amino acids and the reduction of protein degradation induced by
Neuroendocrine hyperactivity characteristic of thermal trauma. Furthermore, an impact was observed.
positive in the healing process of skin lesions, stimulating collagen deposition and...
reorganization of the extracellular matrix, which contributed to the acceleration of tissue repair and to
Reducing the risk of secondary infectious complications.

Another relevant aspect identified refers to the role of oxandrolone as a component.
complementary to a multidisciplinary therapeutic approach. The literature reviewed demonstrates that
Its effects are enhanced when combined with early high-protein nutritional support, to
pharmacological control of the hypermetabolic response and the implementation of structured programs
physical rehabilitation, showing that isolated intervention has a more limited impact.
when not integrated into combined therapeutic strategies.

Despite the consistency of the findings related to the preservation of muscle mass and to
Regarding improvements in functional recovery, disagreements remain in the literature concerning the impact of...
oxandrolone and its effects on major clinical outcomes, such as mortality and total length of hospital stay.
hospital-based studies, possibly due to methodological heterogeneity among the studies.
available, including differences in therapeutic protocols, administered doses, and...
clinical characteristics of the populations evaluated.

Thus, the results of this review reinforce that oxandrolone constitutes a
a promising adjuvant therapeutic strategy in the management of the hypermetabolic state associated with
severe burns, especially when used early and under clinical supervision.
adequate.

However, the need for more controlled clinical trials is highlighted.
methodological standardization that allows the establishment of defined therapeutic protocols regarding
ideal dose, timing of administration, and impact on long-term clinical outcomes.
contributing to the consolidation of its role in evidence-based clinical practice.

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