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# Glucocorticoid-mediated skeletal muscle atrophy: molecular mechanisms and potential therapeutic targets - Evidence review

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## 1. ABSTRACT

The analyzed publication is a narrative review of the mechanisms by which glucocorticoids, including dexamethasone, can promote muscle mass loss. The objective is to describe how these hormones or drugs reduce the signals that support protein synthesis and increase the expression of genes involved in muscle protein degradation. It does not present a new clinical or cellular experiment, but synthesizes studies published between 2010 and 2025.In paragraph 4.14 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the publication contributes to the passage stating that dexamethasone, in myoblasts, activates catabolic programs and suppresses the anabolic signal mediated by AKT. Independent studies in muscle cells confirm that dexamethasone can reduce the phosphorylation of AKT and downstream signals, increase genes such as MuRF1 and atrogin-1, and hinder the formation of muscle fibers. However, these data derive primarily from cellular models and do not, by themselves, demonstrate that every clinical exposure to glucocorticoids causes the same effect, with the same intensity, in all patients.

ONLINE ARTICLE

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Through articles, reviews, in-depth analyses and expert contributions, the Journal champions evidence-based medicine and science, fostering a correct interpretation of scientific data and countering misinformation. Every piece of content is developed with the aim of translating the complexity of research into understandable, useful and applicable information, while keeping intact the principles of accuracy, transparency and scientific independence.

Free from political, industrial and commercial influence, the journal stands as an authoritative and independent editorial space, dedicated to promoting scientific culture, professional development and the growth of health awareness among the public.

## 2. ANALYZED STUDY

The research question concerns how prolonged exposure to glucocorticoids can reduce muscle mass. Glucocorticoids are stress hormones, such as cortisol, but also include anti-inflammatory drugs like dexamethasone. The publication examines the hypothesis that these compounds alter the balance between protein synthesis and degradation in muscle fibers: by reducing insulin and insulin-like growth factor signaling, they increase protein degradation.The relevance to paragraph 4.14 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi is specific. The book states that, in myoblasts, dexamethasone activates catabolic genes and suppresses the anabolic signal mediated by AKT. AKT is a signaling protein that, when activated, promotes protein synthesis and limits certain cellular degradation programs. The analyzed publication describes this very segment of the chain: glucocorticoid reduction of the PI3K/AKT/mTOR signal activation of atrophy genes loss of muscle protein.Since this is a literature review, the work cannot directly demonstrate a causal relationship in humans. However, it can integrate previously published experimental results and indicate which mechanisms are most consistent across cellular studies, animal models, and available clinical data.

## 3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The publication is a narrative review of the literature, not an experimental study conducted on new participants, animals, or cell cultures. The authors declare that they searched for works published from 2010 to 2025 in biomedical databases and a clinical trial registry, using terms related to muscle atrophy and glucocorticoids.The available material does not report a pre-registered protocol, a comprehensive reproducible search strategy, the total number of records identified, formal inclusion and exclusion criteria, or a systematic assessment of the risk of bias for the selected studies. Therefore, there is no overall sample size, single follow-up, predefined endpoints, or quantitative meta-analysis available.The authors discuss studies on muscle cells, animals, and humans, focusing on biological pathways involved in protein synthesis and degradation. These include PI3K/AKT/mTOR, a signaling sequence that promotes protein construction; FoxO, a family of factors that can activate catabolic genes; and MuRF1 and atrogin-1, proteins that tag other muscle proteins for breakdown.

## 4. RESULTS

The central finding of the review is that excessive or prolonged exposure to glucocorticoids can shift muscle toward a negative balance: fewer proteins are produced and more are degraded. According to the authors' summary, the glucocorticoid receptor reduces the activity of the PI3K/AKT/mTOR pathway, which is fundamental for translating nutrients and growth signals into protein synthesis.In molecular terms, the review reports that dexamethasone can reduce IRS-1, a protein that transmits the initial signal of insulin and growth factors inside the cell. It can also increase REDD1 and KLF15, regulators associated with the inhibition of mTORC1, the complex that stimulates the initiation of protein synthesis. The proposed biological consequence is a reduced capacity of the muscle cell to build and maintain contractile proteins.In parallel, the reduction in AKT activation can promote the nuclear activity of FoxO factors. In simple terms, a brake on cellular programs that increase protein turnover is removed. The review links this event to an increased expression of atrophy genes, including MuRF1 and atrogin-1, which participate in the ubiquitin-proteasome system—the mechanism that tags and degrades selected proteins.The work emphasizes that fast-twitch fibers, which are more dependent on glucose metabolism, seem particularly sensitive to the catabolic effects of glucocorticoids. However, the publication does not report a single quantitative average effect, an aggregate estimate of clinical risk, or data that would allow for the precise prediction of muscle loss in a person treated with dexamethasone.

## 5. INTERPRETATION

The practical significance of this narrative is that a glucocorticoid does not act solely as an anti-inflammatory drug: in muscle cells, it can also modify the signals that regulate how many proteins are produced and how many are broken down. Regarding the passage cited in the book, the most important segment is the combined effect on AKT and catabolic genes.The proposed chain of events is

biologically plausible. If AKT is less activated, mTOR receives fewer signals favoring protein synthesis. At the same time, FoxO can contribute to the increase of MuRF1 and atrogin-1, two components of the protein degradation system. The expected result is greater vulnerability of the muscle fiber to atrophy, that is, to a reduction in size and protein content.The publication subject to this Evidence Review documents this framework primarily through the synthesis of preclinical studies. It does not demonstrate that dexamethasone compromises AKT in the same way in every human muscle, nor that the activation of a single catabolic gene is sufficient to explain all atrophy. Furthermore, dosage, duration of exposure, nutritional status, inflammation, and muscle fiber type can modify the response.

## 6. INDEPENDENT CONFIRMING EVIDENCE

Direct confirmation of the process involving myoblasts comes from a study on murine C2C12 cells, muscle precursor cells frequently used to observe myotube formation. Cortisone and dexamethasone, at concentrations between 0.01 and 1.0 micromolar, reduced myotube formation in a dose-dependent manner. With dexamethasone at 1.0 micromolar, the average length of the myotubes decreased from 3.68 to 0.31 millimeters. In the same model, the catabolic genes MuRF1 and atrogin-1 increased, while the phosphorylation of AKT and signals involved in protein synthesis decreased. This confirms, in a cellular model, both the increase in degradation programs and the reduction of the anabolic signal [1].A second independent study evaluated the role of the glucocorticoid receptor in C2C12 cells with reduced expression of the receptor itself. Dexamethasone induced a decrease in AKT activity, an increase in FOXO1 activity and the expression of MAFbx—another name for atrogin-1—along with an increase in protein catabolism. The reduction of the glucocorticoid receptor attenuated these responses. The result supports an experimental causal link between receptor activation, reduction of the AKT signal, and induction of atrophy genes, although it remains limited to a murine cellular system [2].A third study observed C2C12 cells exposed to dexamethasone for different durations. After 36 hours, the treatment significantly reduced protein synthesis, as well as the phosphorylation of mTOR and the p70S6K protein, a signal downstream of mTOR that promotes protein production. In the same experiment, MuRF1 RNA and protein increased, while atrogin-1 RNA increased without a detectable increase in its protein. This finding reinforces the general direction of the narrative but also shows that catabolic genes do not all respond in the same way and at the same time [3].Taken together, these independent studies converge on the fact that dexamethasone can reduce anabolic signals and increase at least part of the catabolic program in muscle cells. However, the strength of this confirmation is primarily mechanistic: the experiments use murine cell cultures and are not designed to estimate the frequency, severity, or reversibility of atrophy in humans.

## 7. CONFLICTING EVIDENCE

Research on C2C12 cells exposed to a high concentration of dexamethasone, 100 micromolar, confirms an increase in MuRF1 and a reduction in mTOR phosphorylation. However, it did not detect a significant change in the total amount of AKT and did not observe a detectable increase in the atrogin-1 protein. The authors therefore proposed that, under those experimental conditions, the increase in MuRF1 may also depend on pathways other than the linear AKT-FOXO1 model [4].This evidence does not contradict the general idea that dexamethasone promotes muscle catabolism, but it indicates that the molecular sequence is not rigid. The response may depend on the drug concentration, the duration of exposure, the type of cell analyzed, and the variable measured, such as RNA, total protein, or phosphorylated form. No sufficiently relevant directly conflicting evidence has been identified in humans; this does not prove the absence of contrary results.

## 8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the review from the independent research used to verify the passage of the book regarding dexamethasone, catabolism, and the AKT signal.

### Quadro comparativo

| Reference | Study type | Population or model | Main result | Direction of evidence | Strength of evidence |
|---|---|---|---|---|---|
| Original study | Narrative review | Literature on cells, animals, and clinical studies published between 2010 and 2025 | Synthesizes that glucocorticoids reduce PI3K/AKT/mTOR and promote atrophy genes | biologically consistent evidence | moderate |
| [1] | Cellular | Differentiating murine C2C12 myoblasts | Dexamethasone reduces myotube formation and AKT phosphorylation; increases MuRF1 and atrogin-1 | direct confirmation | moderate |
| [2] | Cellular | C2C12 cells with experimental reduction of the glucocorticoid receptor | The glucocorticoid receptor is necessary for part of the reduction in AKT and the increase in atrogin-1 | direct confirmation | moderate |
| [3] | Cellular | C2C12 cells treated with dexamethasone | Reduction in protein synthesis and mTOR/p70S6K phosphorylation; increase in MuRF1 | indirect confirmation | moderate |
| [4] | Cellular | C2C12 cells exposed to a high dose of dexamethasone | MuRF1 increases and mTOR decreases, but total AKT and protein atrogin-1 do not change significantly | discordant evidence | low |

## 9. SINTESI EDITORIALE E CONCLUSIONI

### CONCLUSIONS

The passage in the book stating that dexamethasone can activate catabolic programs and reduce AKT anabolic signaling in myoblasts is mechanistically supported. Independent cellular studies show a reduction in AKT/mTOR signaling and an increase in protein degradation markers, especially MuRF1 and atrogin-1. However, differences between experiments indicate that the response depends on the biological context and the dose. Translating these results into clinical practice requires further human studies evaluating muscle mass, strength, and function.

Aggiornato al 24/11/2026. Questo contenuto riflette una sintesi divulgativa delle evidenze scientifiche al momento della pubblicazione e non sostituisce il parere medico.

## 10. TRANSPARENCY AND SCIENTIFIC RESPONSIBILITY

Artificial Intelligence was used solely as a tool for editorial and documentary support. All content, interpretations, bibliographic citations and conclusions have been verified, reviewed and approved by the author, who assumes full scientific responsibility for them.

The manuscript was also subjected to independent peer review prior to publication.

To ensure the greatest transparency, the complete history of the article, including the dates of submission, revision, acceptance and publication, as well as information on the peer review process, is available on the dedicated Article History page.

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