# Anabolic and Anticatabolic Agents in Burns

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## 22.1 Introduction

Traumatic injuries such as burns result in a substantial release of inflammatory mediators, which leads to significant metabolic derangements and the introduction of a post-injury stress environment. This hypermetabolic response is characterized by accelerated lipolysis, glycolysis, insulin resistance, organ dysfunction, and proteolysis [1, 2]. If untreated in the acute phase, the net effect of these post-burn changes is physiological exhaustion and organ failure. Long-term alterations and entry into a hypermetabolic state result in immunodeficiency, compromised wound healing, loss of total and lean body mass, and growth retardation in pediatric patients [3].

Particularly, an important feature of the post-burn hypermetabolic response is generalized catabolism. Hypercatabolism can be attributed to a shift in the production of anabolic to catabolic factors. Increased levels of pro-inflammatory cytokines (e.g., tumor necrosis factor (TNF) and interleukin-6 (IL-6)) occur immediately after injury and are intimately associated with augmented catabolic hormones, principally cortisol and catecholamines [4]. Furthermore, hypermetabolism is associated with a suppression of the endocrine axis, which can result in a substantial decrease in serum levels of endogenous anabolic hormones. Indeed, burn patients exhibit diminished levels of hormones such as human growth hormone (hGH), IGF-I, and testosterone post-trauma [5].

Several non-pharmacologic interventions such as exercise, appropriate nutrition, and heating the environment have been employed to manage post-trauma hypermetabolism. While they improve hypermetabolic catabolism, pharmacologic interventions appear critical for clinical efficacy. Various pharmacological strategies have been used to prevent catabolism and promote anabolism in thermally injured patients. This chapter analyzes the anticatabolic and anabolic pharmacologic interventions currently utilized. It covers propranolol, growth hormone (GH), insulin growth factor 1 (IGF-1), insulin growth factor binding protein 3 (IGFBP-3), insulin, metformin, testosterone, oxandrolone, and thyroid hormones. Furthermore, novel therapeutics utilized in other conditions, such as cancer-related cachexia, are discussed. These agents may potentially be used to mitigate post-injury catabolism and bolster anabolic responses, ultimately improving morbidity and mortality in burn and critically ill patients.

## 22.2 Propranolol

Substantial catecholamine production occurs after burns, with sustained increases persisting for months after the inciting injury [1, 2]. Prolonged elevation in catecholamine levels is a major contributor to the post-burn hypermetabolic response. Elevated catecholamine levels result in a hyperdynamic circulation, increased resting energy expenditure (REE), lipolysis, and muscle catabolism, to list a few downstream effects [6]. Additionally, catecholamines contribute to the generalized catabolic response seen in burn patients via stimulation of both α and β receptors.

Propranolol, which is a non-selective β-blocker, attenuates this hyperactive sympathetic response. Ideally, it should

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be administered post-resuscitation (3–10 days after burn) to mitigate the hypermetabolic response and aid in recovery [7]. In adults, starting doses are 10 mg TID until a 20% reduction in heart rate is achieved. In pediatric patients, propranolol is given at 1 mg/kg/day and escalated to ~4 mg/kg/day to achieve a 20% reduction in heart rate [8]. Recent studies demonstrated that propranolol use was associated with improved wound healing, decreased healing time and blood loss during skin grafting, and shorter hospital length of stay (LOS) [9]. Manzano-Nunez et al. conducted a systematic review and meta-analysis of propranolol therapy in severely burned (TBSA > 20%) adults and children. The included studies demonstrated decreased requirements for blood transfusions and decreased heart rate in propranolol-treated patients [10]. Administration of propranolol to severely burned patients reduces cardiac work by a 15–20% reduction in heart rate [11–13]. Similarly, use of other beta blockers that are comparable to propranolol, such as esmolol, demonstrates beneficial sympathetic effects in critically ill patients in septic shock with post-resuscitation tachycardia. In these patients, propranolol decreases cardiac workload, which reduces mortality by 40% [14].

In addition to its direct sympathetic effects, propranolol prevents peripheral lipolysis and proteolysis by mitigating catecholamine signaling and reducing resting energy expenditure [1, 2, 15, 16]. Hart and colleagues further elucidated the anticatabolic effect of propranolol during the early post-burn hypercatabolic stage. They compared treatment with propranolol to a combination of propranolol and recombinant human growth hormone (rhGH) in severely burned (TBSA > 40%) children, demonstrating that propranolol is a potent anticatabolic agent. Additionally, association with rhGH did not produce a synergistic positive effect [15]. Furthermore, Jeschke and colleagues compared the outcomes with rhGH with propranolol versus rhGH alone. They demonstrated that combination therapy mitigates hypermetabolism and inflammation and ameliorates the deleterious effects found with rhGH monotherapy [16]. In addition to its anticatabolic function, propranolol has anabolic effects as well. Herndon et al. previously demonstrated that propranolol therapy in severely burned (>40% TBSA) children increases net muscle–protein balance by 82% over baseline, with a significant upregulation in genes involved in muscle metabolism [11]. Also, propranolol does not compromise exercise-induced enhancements in muscle mass, strength, and peak aerobic capacity in children with >30% TBSA [17].

Moreover, prolonged administration of propranolol has multiple beneficial effects. Patients receiving propranolol for 1 year post-injury demonstrated significant reductions in bone loss, decreased predicted heart rate, and REE [18]. Prolonged therapy is safe and does not increase incidence of infections or sepsis, highlighting the benefit of long-term therapy with this anticatabolic agent [18–21].

However, Martinez et al. recently proposed in a small series of cases that use of propranolol with vasopressors in septic shock could predispose patients to intestinal ischemia. They postulated that endogenous catecholamine release during hypotensive and septic periods in concert with β-blockade could lead to unopposed α-adrenergic activity. This in turn would impair circulation via severe splanchnic vasoconstriction and lead to bowel ischemia [22]. Taken together, these results highlight the potential risks of propranolol. Other potential side effects include hypotension and bradycardia; however, both can easily be diagnosed and managed in a burn intensive care unit.

Despite these potential negative effects, there is ample evidence for the benefits of propranolol therapy. However, this evidence is primarily limited to pediatric patients, and there is insufficient published data demonstrating these effects in adults and elderly patient [23, 24]. Currently, there is no published randomized controlled data in adult burn patients indicating metabolic benefits of non-selective β-blocker therapy. Further studies are needed to establish propranolol therapy as an effective means to improve outcomes in adult burn patients [25–27]. Ongoing randomized control trials sponsored by the American Burn Association are currently investigating efficacy of propranolol on burn outcomes in these patients.

*Summary: While there is limited evidence in adult and elderly burn patients, current studies suggest that propranolol could effectively decrease stress responses and be a useful anticatabolic agent in pediatric burn patients, as well as adult burn patients. The dose range is in children: 1–4 mg/kg/day and in adults 10–40 mg QID P.O.*

## 22.3 Recombinant Human Growth Hormone

Human growth hormone (hGH) is an endogenous anabolic hormone produced by the pituitary gland in children and young adults. The pituitary gland produces approximately 0.5–0.8 mg of hGH daily, which associates with a variety of GH binding proteins and receptors in various tissues [28]. In GH-deficient children, recombinant human growth hormone (rhGH) therapy has been employed to increase body cell mass and stimulate bone formation [29]. Disruption in the GH/insulin-like growth factor-1 (IGF-1)/IGF binding protein-3 (IGFBP-3) hormone axis are known to occur after burn, potentially due to the inhibitory effects of proinflammatory cytokines, which are overexpressed post-burn [30]. In these cases, daily intramuscular injection of the anabolic agent rhGH is an attractive option to counteract the catabolic effects of burn injury.

Treatment outcomes with rhGH have been comprehensively studied in children and adult burn patients. As

mentioned earlier, Hart and colleagues investigated the effects of up to 1 year post-injury treatment with 0.05 mg/kg/day rhGH in children with burns >40% TBSA. This study showed more pronounced weight and height gain, higher lean body weight, and bone mineral density with rhGH treatment compared to placebo [15]. An adult study by Kim et al. demonstrated that a 3-month rhGH treatment in patients with full thickness burns greater than 20% TBSA had a positive effect on fitness, muscle power, and other metabolic processes [31]. Similarly, Branski and colleagues demonstrated improved growth and lean body mass with rhGH treatment, while hypermetabolism was significantly diminished [32]. Additional studies by Jeschke et al. also demonstrated attenuated post-burn hypermetabolic and hyperinflammatory responses, notably when utilized as a combination with propranolol [16].

Long-term treatment with rhGH has multiple putative effects; for example, it can increase thyroid hormone-binding sites, which may be involved in the growth arrest seen in post-burn children [33]. Other studies have shown that rhGH ceases growth arrest in thermally injured children, decreases REE, and decreases cortisol levels and the acute phase proteins, TNF-α and IL-1. Also, rhGH is not a risk factor for hypertrophic scar formation; Branski and colleagues showed that rhGH treatment significantly improved scarring 1 year post-burn [32].

A Cochrane systematic review published in 2012 on the implementation of rhGH in thermally injured patients appraised 13 randomized controlled trials (totally 701 adult and pediatric patients). Primary outcomes included healing of the burn wound and donor sites and rates of wound infection, and secondary outcomes were mortality, hospital LOS, scar assessment, and adverse events such as hyperglycemia or septicemia. The review demonstrated that there is evidence that rhGH use in large burns (>40% TBSA) could induce more rapid wound healing in adults and children and reduced hospital LOS without an increase in mortality [34].

However, the 2012 Cochrane review showed that rhGH treatment is associated with increased hyperglycemia. While the conclusions of this review were based on studies with smaller sample sizes, which introduces the risk of bias, increased hyperglycemia is a potential concern. Additionally, the beneficial outcomes seen with rhGH treatment in burn patients, such as improvement in muscle protein kinetics, donor site healing, and REE, are not translatable in critically ill, non-burned patients. A prospective, multicenter, double-blind, randomized, placebo-controlled trial of 0.10 ± 0.02 mg/kg rhGH in 285 critically ill non-burned patients was associated with a 40% increase in morbidity and mortality, hyperglycemia, and insulin resistance [35]. So, while rhGH does seem to have a positive anabolic effect, the concern for hyperglycemia, decreased effectiveness in non-burned, critically ill patients, and lack of an oral formulation limit its use.

*Summary: While it may have some beneficial effects, rhGH should be very carefully considered and is currently not a standard of care in burn or critically ill patients. RhGH should not be administered in the state of infection or sepsis.*

## 22.4 Insulin Growth Factor 1 (IGF-1) and Insulin Growth Factor Binding Protein 3 (IGFBP-3)

The anabolic effects of hGH are mostly modulated by IGF-1, which is produced by the liver in response to GH. IGF-1 is a polypeptide with a sequence similarity to proinsulin. More than 95% of IGF-1 is bound to an IGFBP 1–6; its principle binding protein is IGFB-3 [36].

Critically ill burn patients characteristically have reduced circulating IGF-1, which could be attributed to alterations in IGF-1 clearance. Indeed, IGF-1 has a shorter half-life when administered to patients after a major surgery compared to healthy controls [37]. This is potentially due to lower levels of IGFBPs, especially reductions in IGFBP-3 levels. During traumatic injuries and in hypermetabolic states, IGF-1 improves the metabolic rate, gut mucosal function, and wound healing and attenuates protein loss by mediating GH [38].

For up to 3 years post-burn, pediatric patients have persistently lower serum IGF-1 and IGFBP-3 levels, which is associated with severe growth arrest [39]. Thus, anabolic agents such as IGF-1 are putatively beneficial in these patients. Wolf and colleagues investigated the effects of exogenous IGF-1 treatment on Th1/Th2 cytokine profiles in mononuclear cells. Compared to controls, they found depressed Th1 and exaggerated Th2 cytokine responses in all burn patients. Interestingly, exogenous IGF-1/IGFBP-3 treatment can partly reverse this response [40]. Likely, the IGF-1/IGFBP-3 complex balances pro- and anti-inflammatory cytokines, which results in improved organ function. This treatment can also attenuate the type I and type II hepatic acute phase response, improving serum levels of constitutive proteins that modify hypercatabolic responses [30, 41–43].

However, while both rhGH and IGF-1 could mediate post-burn hypermetabolism and generalized catabolism in burn patients, their use has been limited due to side effects, namely hyperglycemia with rhGH and hypoglycemia with IGF-I [44]. Additionally, IGF-1 as a monotherapy should be avoided as Langouche and Van den Berghe showed that IGF-1 alone lacks efficacy in critically ill, non-burned patients [45]. However, since the effects of GH are mediated by IGF-1 and IGFBP-3, IGF-1 combined with equimolar doses of IGFBP-3 is another potential treatment option. Combination therapy of IGF-1/IGFBP-3 at doses of 1–4 mg/kg/day in severely burned children was shown to improve

protein fractional synthetic rate and net protein balance. Debroy et al. showed a similar effect in severely burned adult patients and concluded that dual therapy may be effective in reducing catabolism [46]. Importantly, improvement in protein synthesis with combination therapy occurs with fewer hyperglycemic incidences than patients given rhGH and with fewer hypoglycemic incidences than IGF-1 treatment alone [1, 2, 41, 42, 47]. However, the IGF-1/IGFBP-3 complex used in the study by Debroy et al. was associated with adverse events such as neuropathies, currently precluding their use in a clinical setting.

*Summary: There is limited evidence in favor of IGF-1 monotherapy or IGF-1/IGFB-3 complex therapy.*

## 22.5 Insulin

Insulin is an effective anabolic and anticatabolic hormone that is utilized as an antihyperglycemic in severely burned patients. Jeschke et al. conducted a large cohort study demonstrating that insulin should be given at doses that achieve a glucose target of 130 mg/ds in pediatric burn patients [48, 49]. In general, critical care literature recommends doses that maintain a blood glucose range of 90–140 mg/dL in burn patients [50]. In addition to its glucose regulating effects, insulin is an attractive agent due to its added ability to increase muscle protein synthesis, accelerate donor site healing, and mitigate lean body mass loss [12, 13]. While its capability of reducing protein degradation is unequivocal, there is still debate regarding the underlying mechanism and the dose required to produce these anticatabolic effects. Insulin likely mitigates protein breakdown at lower doses and stimulates protein synthesis at higher doses [51].

Van den Berghe et al. suggest that this suppression of proteolysis and activation of protein synthesis is at least partly facilitated by an increase in serum IGF-1 levels [52]. However, intensive insulin therapy (IIT) in critically ill non-burned patients results in further suppression of serum IGF-1, IGFBP-3, and other GH-binding protein levels, with a corresponding increase in circulating GH [53]. Presumably, insulin primarily exerts its anabolic effects by suppressing IGFBP-1, thereby increasing the bioavailability of IGF-1. Thus, the fact that IIT did not affect IGFBP-1 levels in critically ill patients could explain why the anabolic effects of insulin did not appear to have a major positive effect on outcomes [52]. Additionally, IIT does not counteract catabolism associated with critical illness; however, it can improve the overall outcomes in pediatric ICU patients [54, 55]. In a subpopulation of critically ill pediatric cardiac surgical patients, insulin administration to achieve normoglycemia similarly did not significantly impact skeletal muscle degradation [56]. Contrarily, high doses of insulin or insulin with amino acid supplementation can restore anabolism in cardiac surgical patients [57].

In critically ill burn patients, Jeschke et al. demonstrated that insulin increases the anabolic factor IGF-1 and IGFBP-3 and mitigates hypermetabolism [19–21, 58]. Gore et al. studied the effects of insulin on skeletal muscle in patients with burns greater than 40% TBSA, demonstrating that hyperinsulinemia increases leg blood flow and the rate of muscle protein synthesis [59, 60]. Additionally, similar work by Ferrando et al. showed that a submaximal insulin dose, which would minimize the risk of hypoglycemic episodes, could actually elicit muscle anabolic effects [61]. Fram et al. aimed to elucidate the mechanism by which IIT is beneficial in an acute pediatric burn unit setting. Their results suggested that IIT treatment decreases REE and improves mitochondrial oxidative capacity and insulin sensitivity in these patients [62].

Despite its utility as an anabolic agent, several studies that were conducted to establish a clear survival benefit with insulin presented conflicting mortality data in both pediatric and adult burn patients. However, there is a consensus that insulin treatment decreases infection rates, sepsis, and organ failure [48, 49, 63–65]. While it lacks a significant survival benefit, insulin improves secondary outcomes such as serum glucose levels and seems to be beneficial as an anabolic agent in burn patients. It is more cost effective than GH or IGF-1 and has a well-established side effect profile, which is only limited to hypoglycemia. However, the risk of hypoglycemia needs to be carefully considered prior to initiating insulin therapy in susceptible patients.

*Summary: Insulin is a safe and cheap anabolic agent with a clear side effect profile. While insulin-induced hypoglycemia is associated with adverse outcomes, insulin currently appears to be an effective agent in regulating muscle catabolism. Insulin can be given to target glucose levels or as a therapy approach to reduce hypermetabolism but glucose levels need to be carefully monitored and/or considered to be given simultaneously.*

## 22.6 Metformin

Metformin is a biguanide that has recently emerged as the primary alternative to insulin for hyperglycemia management in severely injured patients [66]. Metformin is administered daily *per os* with a maximum daily dose of 35 mg/kg (2.5 g/day) body weight [67]. Standard formulations require multiple dosing, while metformin XR (extended release) is administered once daily, resulting in better medication regimen adherence [68].

Although the underlying mechanisms are complex and still debated, the downstream effects of metformin are known. It has a dual role in enhancing peripheral insulin sensitivity and regulating gluconeogenesis. Metformin suppresses hepatic glucagon production and thus hyperglycemia

by mitigating the synthesis of cyclic AMP [69]. Cyclic AMP is elevated after thermal injury and is one of the potential mechanisms in the development of post-burn hyperglycemia and insulin resistance. As a result, metformin counters the underlying processes and is an attractive option in managing burn-induced hyperglycemia.

Similar to insulin, metformin may be applicable as both an antihyperglycemic and a muscle protein anabolic agent in critically injured patients. However, the mechanism by which metformin mediates muscle protein balance is still unclear. According to Gore and colleagues, there is a relationship between elevated glucose levels and net muscle protein catabolism. Gore et al. conducted a double-blind, randomized study focusing on peripheral metabolic effects of insulin versus metformin after a severe burn injury. The results showed an increased fractional synthetic rate of muscle protein and improvement in net muscle protein balance in metformin-treated patients [70, 71]. Metformin, therefore, functions as a muscle protein anabolic agent in critically ill patients, likely due to its ability to improve insulin receptor sensitivity and attenuate hyperglycemia. Given that metformin augments insulin sensitivity, it is plausible that metformin and insulin may synergistically function in regulating glucose levels and ameliorating skeletal muscle catabolism.

However, a possible metformin side effect is lactic acidosis or potential worsening of renal failure in susceptible patients [72]. As a result, metformin should not be given in patients with impaired lactate elimination, including those with renal and hepatic failure [73]. In severely burned patients a recent safety and efficacy clinical trial demonstrated no worsening of renal or hepatic function and no incidences of lactic acidosis in burn patients treated with metformin. Additionally, a review of clinical trials on type II diabetic patients also did not have any cases, highlighting the low incidence of lactic acidosis [74]. While no patients had lactic acidosis in the previously mentioned studies, this condition can be effectively managed in the burn ICU setting, making careful administration of metformin a safe alternative to insulin.

Compared to insulin, metformin demonstrates noninferiority in terms of glycemic regulation and anabolic effects and superiority in terms of its antilipolytic effects [75]. Beyond clinical efficacy, there are other benefits such as cost-effectiveness and ease of administration. Metformin is given *per os*, and glucose levels need to be checked less frequently versus insulin once glucose and medication levels are stabilized. Given the clinical benefits and minimal side effects, metformin is an attractive treatment option and an integral component of post-burn care.

*Summary: Metformin effects and its application as an anabolic agent are yet to be comprehensively studied. A recent safety however indicated the efficacy and safety of metformin in burn patients. Dosing should be 500–1000 mg BIP or even TID if no hepatic or renal concern.*

## 22.7 Testosterone

Under the conditions of severe stress, the hypothalamic–pituitary–gonadal axis functions by reducing the signal for the production of testosterone. Burn patients have significant reductions in total and free testosterone levels such that severely burned men have comparable levels of serum testosterone to women [5]. This deficit persists after discharge.

Ideally, restoration of testosterone levels by exogenous therapy should facilitate skeletal muscle anabolism. Ferrando et al. investigated the effects of testosterone treatment at a dose of 200 mg/week IM for 2 weeks in severely burned (>70% TBSA) male patients. They demonstrated that normalizing testosterone levels results in a twofold reduction in muscle protein catabolism with normal feedings [76]. As the protein synthetic rate is maintained, the primary mechanism of action seems to be due to the reduction in skeletal muscle breakdown. Interestingly, while short-term testosterone treatment has similar anabolic outcomes in adult and pediatric burn patients, there is a marked difference in the mechanism of action. As mentioned above, testosterone therapy regulates catabolism in adult burn patients. Alternatively, pediatric patients demonstrate greater muscle protein synthesis rather than decreased catabolism [77, 78].

An important consideration that limits the use of testosterone in burn patients is its side effect profile. Side effects of testosterone therapy include increased risk of cardiovascular events, such as myocardial infarction, coronary artery disease and deep vein thrombosis, hepatotoxicity, erythrocytosis, and prostatic and dermatologic disorders [79]. Additionally, the use of this agent may be limited in women due to its androgenic effects. Owing to its broad side effect profile and the lack of oral methods of administration, alternative agents are preferred to testosterone. This includes its synthetic derivative, oxandrolone, which has a more favorable pharmacological profile.

*Summary: While testosterone may have some beneficial anabolic effects in burn patients, its use is limited due to the risk of adverse events and limited applicability to male patients.*

## 22.8 Oxandrolone

Oxandrolone, which is a synthetic derivative of testosterone, has been successfully implemented in pediatric patients with constitutional delays in growth, cachexia associated with alcoholic hepatitis, and HIV-related catabolic syndrome [80]. Studies in non-burn patients demonstrated enhanced

weight and muscle mass gain, which is optimally augmented with administration of appropriate nutrition.

Previous work in adult burn patients studied the effects of 20 mg/day oxandrolone *per os* a minimum of 2 days post-burn [81]. As outlined in the previous section on testosterone, the mechanism of action differs between pediatric and adult patients. Oxandrolone has primarily an anticatabolic effect in adults and anabolic effect in children [82]. Barrow et al. analyzed the gene expression patterns in skeletal muscle obtained from pediatric burn patients treated with oxandrolone. Interestingly, the authors showed altered expression of 21 genes and increased muscle protein net balance, which was corroborated by muscle biopsies [83]. Similar findings have been seen in other studies as well [84].

Tuvdendorj et al. showed reduced acute phase and increased constitutive protein levels during the acute phase in pediatric patients with burns greater than 20% TBSA [85]. Jeschke et al. conducted a large, prospective, double-blind, randomized single-center study on burn patients to assess the effects of oxandrolone during the acute phase post-burn. The authors demonstrated that oxandrolone shortened hospital LOS, maintained lean body mass, and augmented hepatic protein synthesis [19–21]. Wolf et al. demonstrated similar findings in a multicenter, prospective, randomized, double-blind trial enrolling 81 adults with burns 20–60% TBSA. In this trial and other similar studies, oxandrolone therapy also shortened the hospital LOS [86, 87]. Wolf et al. also showed that oxandrolone effectively restored lean body mass in the acute and rehabilitation phase post-burn. Importantly, oxandrolone therapy may potentially be associated with improved survival, theoretically due to its prolonged beneficial effects in the acute and rehabilitation phase [88]. In the latter, 1 year oxandrolone treatment exhibited long-term improvements in lean body mass, bone mineral content, and bone mineral density, significant increases in height and weight, and a decrease in REE. There is further evidence that oxandrolone may also have long-term effects that can persist for up to 5 years post-burn [89].

To provide a consensus, recent meta-analyses have evaluated the use of oxandrolone in thermally injured patients. Real et al. demonstrated decreased lean body mass loss, less negative nitrogen balance, and shorter hospital LOS. However, this meta-analysis excluded pediatric patients and included few studies. Most recently, Li et al. conducted a meta-analysis that included 15 randomized controlled trials. While the authors showed that oxandrolone treatment does not affect mortality or the risk of infection, it does shorten hospital LOS, donor-site healing time, and time between surgical procedures. Additionally, oxandrolone mitigates weight and nitrogen loss, resulting in an accrual of lean body mass 6–12 months post-burn [90].

While it is equally as effective in decreasing weight loss and has similar benefits to other anticatabolic agents such as rhGH, oxandrolone has an improved side effect profile. Demling demonstrated this in a randomized, prospective study comparing rhGH and oxandrolone after severe thermal injury. The authors showed that rhGH results in significant hyperglycemia and accentuated hypermetabolism compared to oxandrolone. Additionally, oxandrolone, which is available as an oral formulation, has a similar but more favorable pharmacologic profile to testosterone; it has ten times greater anabolic effects and only 10% of the androgenic effects [91]. However, reversible sexual changes have been noted during oxandrolone therapy in pediatric patients. The most common side effect reported is hepatotoxicity. Previous studies compared liver dysfunction, assessed by liver transaminase levels, in thermally injured pediatric and adult patients [19–21, 92]. However, McCullough et al. demonstrated no significant differences in liver dysfunction between treatment and control groups in adult burn patients, and Miller and Btaiche similarly showed only a mild increase in transaminase levels in pediatric patients [91]. While oxandrolone therapy in severely burned patients during the acute phase and long-term is beneficial, liver function monitoring during treatment is recommended.

*Summary: Oxandrolone is an effective alternative to testosterone therapy. The improved side effect profile and availability of an oral formulation make it an attractive option. Currently recommended as an anabolic agent. Dosing 10 mg BID in pediatrics or adults and 5 mg BID in elderly.*

## 22.9 Thyroid Hormones

Thyroid hormones have overarching effects on growth and energy expenditure. The hypothalamic–pituitary–thyroid axis consists of hypothalamic thyrotropin-releasing hormone (TRH), thyroid-stimulating hormone (TSH) at the pituitary level, and peripheral thyroxine (T4), tri-iodothyronine (T3), and reverse T3. Alterations in the hypothalamic–pituitary–thyroid axis during illness results in a condition known as euthyroid sick syndrome whereby serum levels of thyroid hormones are low in patients without thyroid disease [93]. This is distinct from patients who simply present with hypothyroidism.

In critical care settings, thyroid hormone levels are inversely correlated with biochemical markers of catabolism such as urea production and markers of bone degradation. Moreover, administration of thyroid hormones was shown to reduce markers of catabolism. This challenges the notion that low thyroid hormone levels are an adaptive, protective response to hypercatabolism in prolonged critical illness [94]. Currently, clinical benefits of the active hormone T3 or the prohormone T4 during critical illness remains controversial. In critically ill patients admitted to an ICU for at least 14 days, TRH therapy with GH release peptide has

been used [95]. This study utilized a 1 μg/kg GHRP-2 plus 1 μg/kg TRH bolus followed by a continuous infusion of 1 μg/kg/h GHRP-2 plus 1 μg/kg/h TRH. Potentially, this may stimulate and maintain pulsatility, responsiveness, and feedback inhibition of GH and TSH secretion, inducing a shift toward anabolic metabolism.

However, there is limited data on the utility of thyroid hormone replacement in burn patients. In fact, giving T3 has little to no effect on recovery rate or rates of deaths from pneumonia and sepsis in these patients. Additionally, thyroid hormone replacement does not mitigate hypermetabolism or the elevated catecholamine levels seen after burn injury. This suggests that in burn patients, hypermetabolic responses are primarily under sympathetic regulation rather than thyroidal adaptive mechanisms. Additionally, there is a concern that administering T3 can increase the incidence of arrhythmias because of the known association between hyperthyroidism and tachyarrhythmias [96].

*Summary: At this time, there is insufficient data to demonstrate efficacy with exogenous thyroid hormone therapy in euthyroid critically ill patients. Thyroid hormones can be considered when low thyroid levels are present.*

## 22.10 Novel Treatment Strategies

Currently, there are alternative novel anticatabolic agents available. However, it is important to note that their indication as anabolic agents have been tested in very specific patient populations; for example, patients with cancer cachexia and other muscle wasting disorders. Importantly, none of these medications have been tested for thermally injured or critically ill patients. Therefore, they require further investigation prior to implementation as anticatabolic agents in these patients.

*Enobosarm* is a nonsteroidal selective androgen receptor modulator that was first developed in 1998. It functions directly by activating muscle androgen receptors and indirectly through non-muscle androgen receptor pathways, which are mediated by muscle fibroblasts [97]. Preliminary studies suggest that treatment with enobosarm at a dose of 3 mg/day induces significant improvements in lean body mass [98]. When tested in healthy elderly men and menopausal women, enobosarm showed a substantial enhancement in physical function [99]. Potentially, it can be utilized in muscle wasting and cachexia secondary to cancer, COPD, heart failure, AIDS, and end-stage liver and renal diseases [100–102]. Clinical trials suggest that the drug is well tolerated, with no difference in the incidence of adverse events between placebo and treatment groups. Adverse events are mild and most commonly include back pain, fatigue, nausea, diarrhea, and flu-like illness.

*Ghrelin*, which is a peptide hormone primarily produced by the gastrointestinal mucosa, induces release of GH from the pituitary gland. Production of ghrelin stimulates energy intake and inhibits expenditure, which creates a positive net energy balance and results in weight gain. A potent, selective ghrelin receptor agonist, *anamorelin*, is an alternative option to exogenous ghrelin. It has a longer half-life than ghrelin and comes in oral formulations as well, with doses typically ranging from 50 to 100 mg daily [103]. Anamorelin was previously tested in cancer-related cachexia, and it showed a positive clinical response profile. Specifically, these patients had sustained increases in lean body mass and appendicular lean body mass (a surrogate of muscle mass), improved measures of muscle strength, and a better quality of life. However, common adverse effects associated with anamorelin include hyperglycemia, nausea, and dizziness. While the previously mentioned trials are promising, further investigation into efficacy and safety are still needed [97, 104–108].

Another important target in the management of skeletal muscle cachexia is the β-adrenergic signaling pathway, which has a crucial role in regulating protein synthesis and degradation. A newer generation β-agonist, *formoterol*, elicits an anabolic response even when given at very low doses of 80 μg daily. Additionally, medications such as formoterol have reduced collateral effects on the cardiovascular system compared with older generation β-agonists (e.g., fenoterol and clenbuterol). However, these agents may still possess some adverse cardiovascular side effects common to β-agonists, highlighting the importance of further research and refinement [109, 110].

## 22.11 Conclusion

Critically ill and thermally injured patients exhibit common aspects during the course of their illness, which are primarily components of hypermetabolism. These clinical features include hyperglycemia and insulin resistance, hyperinflammation, catecholamine surges, and generalized catabolism. Importantly, these injury-related consequences can occur years after the acute phase, necessitating the implementation of pharmacological interventions. Currently, many pharmacological agents have been studied to improve morbidity and mortality in these patients. This chapter focuses on anticatabolic and anabolic medications, which function through a variety of mechanisms to shift the balance from muscle breakdown to muscle synthesis.

Of the drugs reviewed, insulin is the primary one that is widely utilized in burn patients. There is a plethora of studies demonstrating its safety and efficacy both as an antihyperglycemic and as an anabolic agent. Metformin is an alternative antihyperglycemic to insulin that has the potential as an anabolic agent. However, the mechanism by which

metformin mediates muscle protein balance is still unclear. Additionally, trials investigating adverse outcomes in burn patients are limited in size, warranting additional studies prior to broad implementation.

Propranolol is another promising anabolic agent with additional anticatabolic features. Namely, it prevents peripheral lipolysis and proteolysis by mitigating catecholamine signaling. Importantly, dual therapy with propranolol and rhGH diminishes hypermetabolism and inflammation and ameliorates the deleterious effects found with rhGH monotherapy. There is currently ample evidence for the benefits of propranolol therapy in pediatric patients. However, there is insufficient published data demonstrating similar effects in adult and elderly burn patients.

Outcomes of rhGH treatment have been comprehensively studied in children and adult burn patients, with higher lean body weight and bone mineral density compared to placebo. Additionally, rhGH treatment attenuates the post-burn hypermetabolic and hyperinflammatory responses, particularly when combined with propranolol. However, rhGH is associated with hyperglycemia, and the beneficial outcomes seen in burn patients are not translatable in critically ill, non-burned patients. Combination therapy of IGF-1/IGFBP-3 in severely burned children similarly improves net protein balance, with an analogous effect in severely burned adult patients. However, the IGF-1/IGFBP-3 complex is associated with adverse events such as neuropathies, currently precluding their clinical use.

Testosterone also demonstrates some beneficial anabolic effects in burn patients, but its use is limited due to the risk of adverse events and limited applicability to male patients. Oxandrolone is an attractive alternative to testosterone therapy with an improved side effect profile. Treatment is beneficial during acute phase and rehabilitative phase, and long-term treatment can increase lean body mass 6–12 months post-burn. However, while oxandrolone shows great promise, it is currently not a gold standard therapy.

While many of the drugs discussed in this chapter are encouraging, they require additional investigation. Thyroid hormones and the other novel therapeutics have some favorable results, but many of the recent studies using these drugs are in non-burned patients. As a result, they cannot be implemented in burn and critically ill patients at this time. Future studies are necessary to expand the repertoire of anticatabolic and anabolic agents in use in burn management.

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**Summary Box**

The anabolic and anticatabolic agents have entered the clinical arena to treat hypermetabolic and catabolic responses after burn. Frustratingly, there is a very little evidence on what to do and what to use. Human growth hormone and IGF-1 have somewhat failed to substantiate initial findings. Insulin and metformin seemed to be novel avenues that have endocrine as well as paracrine effects that could improve systemic metabolic responses. Testosterone and oxandrolone are quite impactful, and at this time, oxandrolone should be preferred over testosterone, due to testosterone side effects. We believe that novel avenues, including thyroid hormones or other anabolic agents, may be introduced to effectively treat hypermetabolic and hyperinflammatory, as well as hypercatabolic, responses. Some of those agents may be even very much upstream, for example, centrally acting.

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