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Review

Anabolic and anticatabolic agents used in burn care: What is known and what is yet to be learned

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ABSTRACT

Major thermal injury induces profound metabolic derangements secondary to an inflammatory "stress-induced" hormonal environment. Several pharmacological interventions have been tested in an effort to halt the hypermetabolic response to severe burns. Insulin, insulin growth factor 1, insulin growth factor binding protein 3, metformin, human growth hormone, thyroid hormones, testosterone, oxandrolone, and propranolol, among others, have been proposed to have anabolic or anticatabolic effects. The aim of this broad analysis of pharmacological interventions was to raise awareness of treatment options and to help establishing directions for future clinical research efforts. A PubMed search was conducted on the anabolic and anticatabolic agents used in burn care. One hundred and thirty-five human studies published between 1999 and 2017 were included in this review. The pharmacological properties, rationale for the treatments, efficacy considerations and side effect profiles are summarized in the article. Many of the drugs tested for investigational purposes in the severely thermally injured are not yet gold-standard therapies in spite of their potential benefit. Propranolol and oxandrolone have shown great promise but further evidence is still needed to clarify their potential use for anabolic and anticatabolic purposes.

Contents

Abbreviations: IGF-1, insulin growth factor 1; IGFBP-3, insulin growth factor binding protein 3; IL-1, interleukin 1; IL-6, interleukin 6; IL-8, interleukin 8; IIT, intensive insulin therapy; hGH, human growth hormone; REE, resting energy expenditure; RCT, randomized controlled trial; rhGH, recombinant human growth hormone; TBSA, total body surface area; TNF, tumor necrosis factor.

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1. Introduction

Inflammatory mediators released secondary to major thermal injuries induce profound metabolic derangements, resulting in an abnormal "stress-induced" hormonal environment. An increase in the proinflammatory cytokines tumor necrosis factor (TNF), interleukin-6 (IL-6) and IL-8 and increased oxidative stress are associated with an unbalanced shift towards catabolism, typically characterized by higher serum levels of cathecolamines and cortisol and lower serum levels of human growth hormone and testosterone. The cumulative effect of these profound derangements result in supraphysiologic metabolic rates, including accelerated proteolysis, lipolysis, glycolysis, liver dysfunction, insulin resistance, and loss of total and lean body mass [1,2].

The consequences of such hypermetabolic state are devastating, both in the acute and chronic settings. In the acute phase, physiologic exhaustion leading to multi-organ failure and death may occur if the exaggerated response is left untreated. In the long-term, the hypermetabolic state may lead to progressive organ dysfunction, immunodeficiency, impaired wound healing, loss of muscle mass and growth arrest in the pediatric population [3–5].

The metabolic changes following a severe burn injury may be essential for the patient's survival. These changes start immediately after the injury, and ultimately provide the brain and the immune system with fuel and help other organs conserve energy. The abnormal intensity and chronic persistence of the hyper-inflammatory and hypermetabolic response, however, is the culprit for turning this adaptive reaction into a vicious cycle of derangements. The perpetuating factors of the hypermetabolic response have been extensively studied, and are believed to be the same as those first initiated following injury: cathecolamines, stress hormones, and pro-inflammatory cytokines. These derangements may persist for years after the initial injury [6,7].

Over the last decades, several pharmacological interventions have been tested in an effort to halt such hypermetabolic state. Insulin, insulin growth factor 1 (IGF-1), insulin growth factor binding protein 3 (IGFBP-3), metformin, human growth hormone (hGH), thyroid hormones, testosterone, oxandrolone, and propranolol, among others, have been proposed to have anabolic or anti-catabolic effects [8–13]. The aim of this broad analysis of pharmacological interventions is to raise awareness of treatment options and to help establishing directions for future clinical research efforts.

2. Search strategy

A PubMed search was performed using the search terms "clonidine", "human growth hormone", "growth hormone releasing peptide", "insulin", "insulin growth factor 1", "insulin growth factor binding protein 3", "metformin", "oxandrolone", "propranolol", "stanozolol", "testosterone", "turinabol" and "thyroid hormone" in addition to "thermal injury", "burns", and "critical care".

The inclusion criteria were studies published in English, from January 1999 to September 2017. Animal studies, articles about these agents focusing on effects or properties other than anabolism or anti-catabolism, and articles on conditions other than burns were excluded.

3. Results and discussion

The initial PubMed search with the filters for language and publication date resulted in 5803 articles. After application of the exclusion criteria, 135 articles were included in this review. No articles on clonidine, growth hormone releasing peptide, stanozolol or turinabol were included.

The pharmacological properties, rationale for the treatments, efficacy considerations and side effect profiles of the anabolic and anticatabolic drugs are summarized below. Table 1 describes the number of articles included and the resulting groups of agents after the application of the exclusion criteria, and Table 2 [14] outlines the characteristics of the included articles.

3.1. *Propranolol*

Immediately after a major thermal injury, there is a massive increase in circulating catecholamines, which is associated with hyperdynamic circulation, increased resting energy expenditure (REE), lipolysis, hyperglycemia and skeletal muscle protein breakdown [15].

Propranolol is a non-selective β-blocker used to attenuate the hyperactive sympathetic system seen in burned patients. It has been extensively studied in the acute phase of severe thermal injury in the pediatric population. It has been shown

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Table 1 – Inclusion and exclusion of articles and resulting agent groups.

Agent	Key words	Inclusion of articles		Exclusion of articles			Resulting articles	
		Included articles per key word	Total number of included articles per agent	Animal studies	Properties other than anabolism or anti-catabolism	Conditions other than burns	Agent group	Number of articles
Clonidine	Thermal injury Burns Critical care	14 11 167	192	33	127	32	Clonidine	0
Growth hormone	Thermal injury Burns Critical care	34 182 212	428	125	81	203	Growth hormone	19
Growth hormone releasing peptide	Thermal injury Burns Critical care	6 35 55	96	48	14	34	Growth hormone releasing peptide	0
Insulin	Thermal injury Burns Critical care	134 1130 2357	3621	664	2628	288	Insulin	17
Insulin growth factor 1	Thermal injury Burns Critical care	36 221 211	468	201	163	96	Insulin growth factor 1 and Insulin growth factor binding protein 3	8
Insulin growth factor binding protein 3	Thermal injury Burns Critical care	10 50 65	125	44	32	47		
Metformin	Thermal injury Burns Critical care	4 25 106	135	22	70	37	Metformin	6
Oxandrolone	Thermal injury Burns Critical care	7 60 9	76	8	4	20	Oxandrolone	21
Propranolol	Thermal injury Burns Critical care	16 92 79	187	68	45	39	Propranolol	19
Stanozolol	Thermal injury Burns Critical care	0 0 0	0	0	0	0	Stanozolol	0
Testosterone	Thermal injury Burns Critical care	14 75 108	197	58	23	108	Testosterone	2
Turinabol	Thermal injury Burns Critical care	0 0 0	0	0	0	0	Turinabol	0
Thyroid hormone	Thermal injury Burns Critical care	8 46 224	278	61	123	93	Thyroid hormone	1
							Multiple agents	42
Total number of included articles		5803					Resulting number of articles	135

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Table 2 – Description of the included articles.

Agent	Author	Year	Type of article[a]	Level of evidence[b]	Characterisitcs of population[c]
Propranolol	LeCompte et al.	2017	Survey	5	Adult and pediatric burn patients
Propranolol	Porro et al.	2013	RCT	1B	7–18 year-old patients with burns > 30% TBSA
Propranolol	Mohammadi et al.	2009	RCT	1B	16–60 year-old patients with burns 20–50% TBSA
Propranolol	Martinez et al.	2016	Case series	4	10 month and 9 year-old patients
Propranolol	Herndon et al.	2003	RCT	1B	3–18 year-old patients with burns > 40% TBSA
Propranolol	Oláh et al.	2011	RCT	1B	0–17 year-old patients with burns > 40% TBSA
Propranolol	Finnerty et al.	2013	RCT	1B	Pediatric burned patients
Propranolol	Herndon et al.	2012	RCT	1B	Pediatric patients with burns > 30% TBSA
Propranolol	Kobayashi et al.	2011	RCT	1B	0–17 year-old patients with burns > 30% TBSA
Propranolol	Ali et al.	2015	RCT	1B	Adult patients with burns > 30% TBSA
Propranolol	Williams et al.	2011	RCT	1B	Pediatric patients with burns > 30% TBSA
Propranolol	Jeschke et al.	2007	RCT	1B	0–18 year-old patients with burns > 40% TBSA
Propranolol	Brown et al.	2016	Retrospective cohort	4	18–65 year-old patients with burns > 20% TBSA
Propranolol	Herndon et al.	2001	RCT	1B	0–18 year-old patients with burns > 40% TBSA
Propranolol	Manzano-Nunez et al.	2016	Systematic review and meta-analysis	1A	Patients with burns > 20% TBSA
Propranolol	Núñez-Villaveirán et al.	2015	Systematic review	1A	Thermally ill patients of all ages
Propranolol	Guillory et al.	2017	Cohort	2B	Adult patients with burns > 30% TBSA
Propranolol	Rivas et al.	2017	RCT	1B	0–18 year-old patients with burns > 30% TBSA
Propranolol	Flores et al.	2016	Systematic review and meta-analysis	1A	Thermally ill patients of all ages
hGH	Hart et al.	2001	RCT	1B	0–18 year-old patients with burns > 40% TBSA
hGH	Przkora et al.	2006	RCT	1B	0–18 year-old patients with burns > 40% TBSA
hGH	Suman et al.	2003	RCT	1B	7–17 year-old patients with burns > 40% TBSA
hGH	Aili Low et al.	1999	RCT	1B	2–18 year-old patients with burns > 40% TBSA
hGH	Suman et al.	2004	RCT	1B	7–18 year-old patients with burns > 40% TBSA
hGH	Mlcak et al.	2004	RCT	1B	0–18 year-old patients with burns > 40% TBSA
hGH	Losada et al.	2002	RCT	1B	18–65 year-old patients with burns > 40% TBSA and/or >15% TBSA full thickness burns
hGH	Barret et al.	1999	RCT	1B	1–18 year-old patients with burns > 40% TBSA and/or >10% TBSA full thickness burns
hGH	Kim et al.	2016	RCT	1B	Patients with burns > 20% TBSA
hGH	Chrysopoulo et al.	1999	RCT	1B	1–18 year-old patients with burns > 40% TBSA and/or >10% TBSA full thickness burns
hGH	Oliveira et al.	2004	RCT	1B	2–18 year-old patients with burns > 40% TBSA
hGH	Lal et al.	2000	RCT	1B	2–18 year-old patients with burns > 40% TBSA and/or >20% full thickness burns
hGH	Branski et al.	2009	RCT	1B	0–19 year-old patients with burns > 40% TBSA
hGH	Breederveld et al.	2012	Systematic review	1A	Thermally injured
hGH	Connoly et al.	2002	RCT	1B	0–18 year-old patients with burns > 40% TBSA
hGH	Jeschke et al.	2000	RCT	1B	0–18 year-old patients with burns > 40% TBSA and/or >10% TBSA full thickness burn
hGH	Thomas et al.	2004	RCT	1B	0–18 year-old patients with burns > 40% TBSA
hGH	Aili Low et al.	2001	RCT	1B	2–18 year-old patients with burns > 40% TBSA
hGH	Raguso et al.	2001	Review	5	Patients with trauma, burns, status post-surgery, respiratory failure and multi-organ failure
IGF-1/IGFBP-3	Debroy et al.	1999	Cohort	2B	>19 year-old patients with burns > 24% TBSA
IGF-1/IGFBP-3	Hasselgren	1999	Review	5	Thermally injured
IGF-1/IGFBP-3	Jeschke et al.	2002	RCT	1B	<15 year-old with burns > 40% TBSA
IGF-1/IGFBP-3	Wolf et al.	2004	RCT	1B	Burns > 20% TBSA
IGF-1/IGFBP-3	Jeschke et al.	2000	Experimental trial with individuals as their own controls	2B	<15 year-old with burns > 40% TBSA
IGF-1/IGFBP-3	Spies et al.	2002	Experimental trial with individuals as their own controls	2B	<15 year-old with burns > 40% TBSA
IGF-1/IGFBP-3	Herndon et al.	1999	Experimental trial with individuals as their own controls	2B	<15 year-old with burns > 40% TBSA
IGF-1/IGFBP-3	Elijah et al.	2011	Review	5	Thermally injured and critically ill
Insulin	Ferrando et al.	1999	RCT	1B	Patients with burns > 60% TBSA

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Table 2 (continued)

Agent	Author	Year	Type of article[a]	Level of evidence[b]	Characterisitcs of population[c]
Insulin	Zeng et al.	2016	RCT	1B	Patients with deep burns
Insulin	Jeschke et al.	2007	Review	5	Thermally injured
Insulin	Gore et al.	2003	Uncontrolled experimental trial	2B	23–52 year-old patients with burns > 40% TBSA
Insulin	Pham et al.	2005	Retrospective cohort	4	0–18 year-old patients with burns > 30% TBSA
Insulin	Pidcoke et al.	2007	Review	5	Thermally injured
Insulin	Hrynyk et al.	2014	Review	5	Thermally injured
Insulin	Jeschke et al.	2004	Cohort	2B	1–18 year-old patients with burns > 40% TBSA and/or >10% TBSA full thickness burns
Insulin	Fram et al.	2010	RCT	1B	4–18 year-old patients with burns > 40% TBSA
Insulin	Jeschke et al.	2010	RCT	1B	0–18 year-old patients with burns > 30% TBSA
Insulin	Hemmila et al.	2008	Cohort	2B	Thermally ill adult patients
Insulin	Tuvdendorj et al.	2011	RCT	1B	0–18 year-old patients with burns > 30% TBSA
Insulin	Wang et al.	2016	RCT	1B	18–75 year-old patients with deep burns
Insulin	Gore et al.	2002	Experimental trial with individuals as their own controls	2B	Thermally ill adult patients
Insulin	Van der Berghe	2004	Review	5	Critically ill patients
Insulin	Gibson et al.	2009	Cohort	2B	Thermally injured and critically ill patients
Insulin	Deng et al.	2009	Review	5	Patients with severe trauma, burn injury and sepsis
Metformin	Gore et al.	2005	Experimental trial with individuals as their own controls	2B	Adult patients with burns > 40% TBSA
Metformin	Jeschke et al.	2016	RCT	1B	Adult patients with burns > 20% TBSA
Metformin	Gore et al.	2005	RCT	1B	Adult patients with burns > 40% TBSA
Metformin	Gauglitz et al.	2008	Review	5	Thermally injured
Metformin	Gore et al.	2003	RCT	1B	Adult patients with burns > 60% TBSA
Metformin	Mecott et al.	2010	Review	5	Thermally injured
Testosterone	Ferrando et al.	2001	Experimental trial with individuals as their own controls	2B	Adult patients with burns > 70% TBSA
Testosterone	Spratt	2001	Review	5	Critically ill patients
Oxandrolone	Hart et al.	2001	Cohort	2B	0–18 year-old patients with burns > 20% TBSA
Oxandrolone	Murphy et al.	2004	RCT	1B	0–18 year-old patients with burns > 40% TBSA
Oxandrolone	Wolf et al.	2006	RCT	1B	Adult patients with burns 20–60% TBSA
Oxandrolone	Porro et al.	2012	RCT	1B	0–18 year-old patients with burns > 30% TBSA
Oxandrolone	Barrow et al.	2003	RCT	1B	0–18 year-old patients with burns > 20% TBSA
Oxandrolone	Pham et al.	2008	Cohort	2B	Adult patients with burns > 20% TBSA
Oxandrolone	Wolf et al.	2003	RCT	1B	0–18 year-old patients with burns > 30% TBSA
Oxandrolone	McCullough	2007	Cohort	2B	Thermally ill adult patients
Oxandrolone	Tuvdendorj et al.	2011	RCT	1B	0–18 year-old patients with burns > 40% TBSA
Oxandrolone	Przkora et al.	2005	RCT	1B	0–18 year-old patients with burns > 40% TBSA
Oxandrolone	Miller et al.	2008	Review	5	0–18 year-old patients with burns > 20% TBSA
Oxandrolone	Demling et al.	2003	RCT	1B	Thermally ill adult patients
Oxandrolone	Miller et al.	2009	Review	5	Thermally injured
Oxandrolone	Spiga Real et al.	2014	Systematic review and meta-analysis	1A	Thermally injured
Oxandrolone	Demling et al.	2000	RCT	1B	Adult patients with burns 40–70% TBSA
Oxandrolone	Jeschke et al.	2007	RCT	1B	0–18 year-old patients with burns > 40% TBSA
Oxandrolone	Przkora et al.	2007	RCT	1B	0–18 year-old patients with burns > 40% TBSA
Oxandrolone	Li et al.	2015	Systematic review and meta-analysis	1A	Thermally injured
Oxandrolone	Cochran et al.	2013	Case-control study	3B	Adult patients with burns > 15% TBSA
Oxandrolone	Thomas et al.	2004	RCT	1B	0–18 year-old patients with burns > 40% TBSA
Oxandrolone	Demling et al.	2001	RCT	1B	Adult patients with burns 30–55% TBSA
Thyroid hormone	Stathatos et al.	2001	Review	5	Critically ill patients
Multiple agents	Herndon et al.	2016	RCT	1B	0.5–18 year-old patients with burns > 30% TBSA
Multiple agents	Ipaktchi et al.	2006	Review	5	Thermally injured
Multiple agents	Shea et al.	2003	Review	5	Thermally injured
Multiple agents	Pereira et al.	2005	Review	5	Thermally injured
Multiple agents	Hart et al.	2002	RCT	1B	0–18 year-old patients with burns > 40% TBSA

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Table 2 (continued)

Agent	Author	Year	Type of article[a]	Level of evidence[b]	Characterisitcs of population[c]
Multiple agents	Klein et al.	2006	Review	5	Thermally injured
Multiple agents	Rojas et al.	2012	Review	5	Thermally injured
Multiple agents	Gauglitz et al.	2011	Review	5	Thermally injured
Multiple agents	Jeschke et al.	2008	RCT	1B	0–16 year-old patients
Multiple agents	Demling	1999	RCT	1B	Patients with burns > 50% TBSA or > 25% TBSA with comorbidities
Multiple agents	Murphy et al.	2003	Review	5	Thermally injured
Multiple agents	Ramzy et al.	1999	Review	5	Thermally injured
Multiple agents	Klein	2015	Review	5	Thermally injured
Multiple agents	Diaz et al.	2015	Review	5	Thermally injured
Multiple agents	Ballian et al.	2009	Review	5	Thermally injured
Multiple agents	Demling et al.	2000	Review	5	Thermally injured
Multiple agents	Williams et al.	2009	Review	5	Thermally injured
Multiple agents	Andel et al.	2003	Review	5	Thermally injured
Multiple agents	Herndon	2003	Review	5	Thermally injured
Multiple agents	Pereira et al.	2005	Review	5	Thermally injured
Multiple agents	Ferrando et al.	2007	Review	5	Thermally injured
Multiple agents	Dylewski et al.	2013	Review	5	Thermally injured
Multiple agents	Herndon et al.	2004	Review	5	Thermally injured
Multiple agents	Pereira et al.	2005	Review	5	Thermally injured
Multiple agents	Ching et al.	2011	Review	5	Thermally injured
Multiple agents	Herndon et al.	2016	RCT	1B	0.5–14 year-old patients with burns > 30% TBSA
Multiple agents	Sheridan et al.	2004	Review	5	Thermally injured
Multiple agents	Janssen	2008	Review	5	GH deficiency states
Multiple agents	Stanojcic et al.	2016	Review	5	Hypermetabolic states
Multiple agents	Ferrando	1999	Review	5	Critically ill patients
Multiple agents	Hadley et al.	2002	Review	5	Critically ill patients
Multiple agents	Ellger et al.	2005	Review	5	Critically ill patients
Multiple agents	Jiang et al.	2000	Review	5	Hypermetabolic states
Multiple agents	Van der Berghe	2000	Review	5	Critically ill patients
Multiple agents	Moore et al.	2017	Review	5	Critically ill patients
Multiple agents	Weitzel et al.	2009	Review	5	Critically ill patients
Multiple agents	Wolfe	2005	Review	5	Hypermetabolic states
Multiple agents	Lang et al.	2002	Review	5	Hypermetabolic states
Multiple agents	Demling	2007	Review	5	Hypermetabolic states
Multiple agents	Demling	2007	Review	5	Hypermetabolic states
Multiple agents	Guillory et al.	2017	RCT	1B	0–18 year-old patients with burns > 30% TBSA
Multiple agents	Carroll	2001	Review	5	Critically ill patients

[a] RCT = randomized control trial.
[b] From the Centre for Evidence-Based Medicine, http://www.cebm.net [14].
[c] TBSA = total body surface area.

to decrease resting heart rate, cardiac work and lipolysis, and to increase skeletal muscle synthesis, opposing the catabolic hormonal environment. Treatment with this agent is safe and effective up to 1year after burn, and is not associated with increased risk of sepsis [16–23].

The benefits of propranolol in severely burned children is not limited to the early period after burns. Porro et al. demonstrated, in a study on children with burns greater than 30% of the total body surface area (TBSA > 30%), that propranolol increases the improvement in cardiopulmonary fitness during the rehabilitation phase. Moreover, Rivas et al. recently showed that treatment with propranolol does not interfere in exercise thermoregulation in children who experienced severe burns [24,25].

The effects of propranolol have also been demonstrated on molecular and cellular levels. According to Herndon et al., burned children treated with propranolol show upregulation of genes associated with muscle protein turnover, which correlates to the increased net protein balance [26]. The agent was also shown to downregulate a nuclear enzyme that is associated with critical illness-related cellular necrosis, and to modulate the M2b monocytes, which are associated with increased risk of infections in burned children [27,28].

Propranolol has also been tested in association with other drugs in the pediatric population. In a study comparing the treatment with propranolol to combination of propranolol and recombinant human growth hormone (rhGH) in children with severe burns (TBSA > 40%), Hart et al. demonstrated that propranolol is a strong anticatabolic agent during the early hypercatabolic period after burns, and that the association with rhGH did not result in any synergistic positive effect on the treatment [29]. Jeschke et al. compared the association of rhGH and propranolol versus placebo. They showed that the

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combination of the agents was as effective as rhGH alone, but with a more tolerable side effects profile [30].

Although Martinez et al. postulated that the combination of vasopressors and propranolol in septic burned children may cause splanchnic vasoconstriction and intestinal ischemia, propranolol's most common side effects are easily diagnosed and treated in an intensive care setting: hypotension, bradycardia and bronchospasm [31].

Data on treatment with propranolol in adult burned patients is not as abundant as in children. However, it has been shown to improve wound healing, and shorten healing time and length of hospital stay [32]. It has also been suggested to decrease blood loss during skin grafting procedures [33].

Finally, a systematic review and meta-analysis on the safety and effectiveness of propranolol in severely burned (>20% TBSA) adults and children demonstrated no impact on mortality or incidence of sepsis. However, treatment with propranolol was associated with less blood transfusions and reduced length of hospital stay [34].

It is reasonable, therefore, to postulate that propranolol has well established benefits in mitigating the hypermetabolic state of severely burned children, both in the acute and the rehabilitation phase. However, there is paucity of studies in the adult and elderly populations. Moreover, there is no definitive guideline, in any age population, regarding the appropriate dosage and duration of the treatment [35–38].

Currently, the use of propranolol in the adult burned population is being prospectively trialed (NCT01902810 and NCT01299753). Other ongoing clinical trials on propranolol include a study in burned children who are receiving propranolol vs. placebo for up to 12 months (NCT01957449), and a RCT comparing the long term outcome of burned patients of all ages randomized into 9 different interventional groups — growth hormone, ketoconazole, oxandrolone, propranolol, oxandrolone and propranolol combined, growth hormone and propranolol combined, placebo, intensive hospital exercise program and home exercise program. In this study, each of the interventions are being trialed for up to 2 years after burn (NCT 00675714) [39–42].

3.2. *Testosterone and oxandrolone*

Severe thermal injury induces hypogonadism that extends from the acute phase until weeks after discharge. Because the entire hypothalamic–pituitary gonadal axis is suppressed, testosterone has been supplemented in order to restore skeletal muscle anabolism.

Short-term treatment with testosterone is equally effective in restoring net protein anabolism in both pediatric and adult burn patients. The mechanism of action, however, is different. Whilst in adults testosterone decreases skeletal muscle protein breakdown, it increases protein synthesis in children. The reasons for such difference is not entirely clear, but it seems to be related to the growth state that pediatric burn patients experience, which provides them with a greater capacity for protein synthesis. Testosterone, nevertheless, takes no action on the inflammatory response or on glucose metabolism [43–47].

Testosterone's side effect profile includes cardiovascular events, such as myocardial infarction, coronary artery disease and deep vein thrombosis, hepatotoxicity, erythrocytosis, prostatic and dermatologic disorders. Furthermore, one of testosterone's major limitations is its androgenic effects. There is scant data on the efficacy of testosterone treatment in women given its virilization properties [48].

Due to testosterone's toxicity and side effect profile, as well as the lack of oral formulation, there has been a preference towards oxandrolone, a functional analog of testosterone, but with higher anabolic properties and minimal androgenic effects. Another advantage of this synthetic derivative is its oral bioavailability. Similar to testosterone, its mechanism of action differs in adults and children. In adults, it seems to spare protein from breakdown, whilst in children it stimulates protein synthesis [49,50].

Treatment of severely burned children with oxandrolone has been the focus of a number of clinical trials. Jeschke et al. demonstrated that oxandrolone treatment resulted in a shorter length of hospital stay, decreased lean body mass loss, improved hepatic protein synthesis and no side effects on the hormonal axis after burn. The authors did note, however, an increase in liver enzymes [51].

Oxandrolone has been tested in children with severe burns (>20% TBSA), chronic infection and nutritional depletion, and its anabolic effect has been well documented [52]. In the acute phase, oxandrolone was also shown to significantly increase constitutive proteins and reduce acute phase protein levels [53]. It has been administered up to 1 year after the burn up to 1 year after the burn injury in a similar population, showing sustained benefits in terms of REE, bone mineral content and density, lean body mass and height and weight gain, even after the end of the treatment [54–59]. There is further evidence that its benefits may persist for up to 5 years after burn in the pediatric population [60].

Oxandrolone's molecular effects have also been focus of research efforts. Barrow et al. demonstrated that thermally injured children treated with oxandrolone showed significant differences in skeletal muscle gene expression patterns when compared to a placebo group, and these findings were confirmed by muscle biopsies [61]. Similar results have been reported by Wolf et al. [62].

In a recent randomized controlled trial in severely burned children (>30% TBSA) between 0.5 and 14 years old, Herndon et al. studied the reversal of growth arrest with the combined administration of oxandrolone and propranolol. Through a comparison between 4 groups (control, oxandrolone alone, propranolol alone, and oxandrolone in addition to propranolol), the authors demonstrated that the combination of the drugs improved growth arrest by an average of 84 days, and increased growth rate by an average of 1.7 cm/year. Both differences were statistically significant between the association treatment group and the control group only, suggesting that the combination of the drugs offers an additional synergistic effect to halt the after burn hypermetabolic syndrome [63]. Oxandrolone treatment has also been demonstrated not to have drug interactions with propranolol administration, showing no effects on propranolol plasma concentration, half-life or effect on heart rate [64].

The adult burned population has also been demonstrated to benefit from oxandrolone treatment. Demling conducted a randomized, prospective trial comparing the anabolic and

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healing effects of rhGH and oxandrolone after thermal injury. The author demonstrated that the two drugs were equally effective in decreasing weight and nitrogen loss and in enhancing wound healing. The side effect profiles, however, were significantly different, as rhGH caused frequent hyperglycemic episodes and augmented hypermetabolism, whilst no considerable side effects were noted in the oxandrolone group [65].

Oxandrolone was also shown to significantly shorten length of hospital stay, and to effectively restore body weight and lean body mass both in the acute and rehabilitation phase of thermal injury. According to Pham et al., treatment with oxandrolone might be associated with improved survival [66–71].

The most concerning adverse effect of oxandrolone is hepatotoxicity. However, McCullough et al. compared liver dysfunction, measured by liver transaminases, among thermally injured adults and showed no significant differences in liver dysfunction between treatment and control groups [72]. Another reported side effect is reversible sexual changes during therapy [73]. Contraindications to the treatment are the presence of testosterone hormone sensitive carcinomas such as cancers of the breast or prostate.

Two systematic reviews and meta-analysis have recently addressed the treatment of the thermally injured with oxandrolone. The first one, by Real et al., excluded pediatric patients, and suggested that treatment with oxandrolone preserves body lean mass and nitrogen balance and shortens length of hospital stay. However, the results of this meta-analysis should be carefully interpreted, since the number of included studies was very low [74].

The most recent meta-analysis, by Li et al., included 15 randomized controlled trials, and showed that treatment of the thermally injured with oxandrolone has no impact on mortality or risk of infection, but does shorten length of hospital stay, donor-site healing time, time between surgical procedures and decreases weight and nitrogen loss. The study also demonstrated that oxandrolone shortens the length of hospital stay and decreases weight loss during the rehabilitation phase. Finally, treatment with this agent led to an increased lean body mass at 6 and 12 months after burn. There was no significant difference in liver dysfunction [75].

Treatment with oxandrolone has well established benefits in both pediatric and adult thermally injured patients. Its beneficial effects have been documented not only in the acute setting, but also in the rehabilitation phase of the treatment. Liver function, growth pattern and sexual development should be monitored while the drug is being administered.

3.3. *Recombinant human growth hormone (rhGH)*

Human growth hormone (hGH) is produced by the pituitary gland in children and young adults. It has several metabolic effects in many different tissues. The anabolic effect, however, is the most important one [76].

The effects of recombinant human growth hormone (rhGH) in thermally injured children has been well established. Hart et al. studied the effects of rhGH treatment up to one year after burn. The authors demonstrated that, when compared to controls, the treatment group gained more weight and height, and that lean body weight and bone mineral content was higher [77]. Branski et al. also demonstrated that rhGH attenuates hypermetabolism, improves scarring, growth and lean body mass and decreases REE and cardiac output [78].

Treatment of burned children with rhGH has been shown to decrease cortisol levels; have no effect on pulmonary function or on hepatic acute phase protein changes; lower TNF-α and IL-1 serum levels; decrease REE; and halt the growth arrest experienced by thermally injured children. It does not increase the risk of hypertrophic scar formation and it seems to increase thyroid hormone-binding sites, which may be involved in the after burn growth arrest pathophysiology. Conflicting results have been published about the effect of rhGH on the healing time of donor sites [79–92].

Kim et al. studied adults with full thickness burns greater than 20% TBSA and showed that treatment with rhGH for 3 months during rehabilitation phase increases fitness levels, muscle power and metabolic processes [93].

Growth hormone supplementation and mortality have been the focus of debate in the literature. Although Jeschke et al. demonstrated that rhGH does not increase mortality in children with severe burns, the study of Takala et al. on critically ill non-burned adult patients and its association between rhGH and a significant increase in mortality has raised concerns regarding the effects of rhGH on burn-related mortality [94,95].

The Cochrane systematic review on the use of rhGH in the thermally injured population reviewed 13 randomized controlled trials (701 patients, both pediatric and adults). The authors concluded that the treatment with rhGH in severely burned patients (>40% TBSA) may decrease healing time and length of hospital stay, with no increase in mortality or scarring. There was, however, increased incidence of hyperglycemia [96]. Therefore, whilst rhGH appears to attenuate the hypermetabolic response in children, administration of this drug to adults has proven to cause hyperglycemia and further increase in hypermetabolism.

Although rhGH seems to have positive anabolic effects, the concern for its most common adverse effect (hyperglycemia), its oral unavailability, and its association with increased mortality in critically ill non-burned adult patients limit its use [97].

3.4. *Insulin growth factor 1 and insulin growth factor binding protein 3*

IGF-1 is a polypeptide that has an aminoacid sequence similar to proinsulin and circulates in the blood stream bound to one of the Insulin Growth Factor Binding Proteins (IGFBP-1 to -6), IGFBP-3 being its major constitutive binding protein. IGF-1 is produced by the liver in response to hGH and mediates most of its anabolic effects [98].

Severely burned patients of all ages show decreased IGF-1 and IGFBPs serum levels. In burned children, the lower plasma concentrations of both IGF-1 and IGFBP-3 are associated with the growth arrest they experience up to three years after burn [99–101].

IGF-1 has been studied in the setting of traumatic and thermal injuries, and it has been shown to improve the metabolic rate, gut mucosal function, and wound healing. The

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drug also attenuates lean body mass and protein loss, and the acute phase response. Moreover, treatment with IGF-1 shows less harmful side effects when compared to rhGH treatment [102–104].

IGF-1 has also been studied in association with IGFBP-3. Wolf et al. investigated Th1/Th2 cytokine profiles and cellular proliferation in thermally injured patients, and demonstrated that IGF-1/IGFBP-3 treatment partially reverses abnormal molecular and cellular findings associated with this type of injury [105]. Jeschke et al. concluded that the administration of the drug association attenuates hepatic acute phase response and increases serum levels of constitutive proteins, ameliorating the hypermetabolic state and, thus, improving cardiac, renal and hepatic functions [106–108]. Other authors have shown that the combined treatment improved net protein balance by increasing skeletal muscle protein synthesis [109–111]. However, the IGF-1/IGFBP-3 complex was found to be associated with significant adverse effects, neuropathy being the most severe one.

Although both rhGH and IGF-1 have been demonstrated to attenuate the post-burn hypermetabolism, their side effect profiles prevent their clinical application. Treatments with rhGH and IGF-1 show risks of, respectively, hyperglycemia and hypoglycemia [112]. However, severely burned patients who received IGF-1 in combination with equimolar doses of IGFBP-3, had improved anabolism with milder glycemic fluctuations when compared to rhGH or IGF-1 alone [113,114].

Despite the fact that there have been studies indicating that the supplementation of IGF-1, particularly in association with IGFBP-3, may have some beneficial potential, this complex was used for investigational purposes only. Due to its side effect profile, the drug association has never been available for clinical application.

3.5. *Insulin*

Given at higher doses, insulin greatly increases muscle protein turnover, by simultaneously stimulating protein synthesis and proteolysis. The resultant net protein balance is positive; hence, it is considered an effective anabolic agent [115].

Whereas there is no doubt about its anabolic capacity, the mechanism through which insulin exerts its beneficial effects are not entirely clear. It seems to be associated with a suppressive effect on IGFBPs, leading to an increased bioavailability of IGF-1 [116]. Insulin also decreases the exaggerated inflammatory and immune responses, which explains the reduced mortality shown after intensive insulin therapy (IIT) in the critically ill population [117].

Fram et al. tried to identify the mechanisms underlying the benefits of IIT in an acute pediatric burn unit. They randomized patients between 4 and 18 years old and demonstrated that, in the IIT group, REE was significantly decreased and mitochondrial oxidative capacity and insulin sensitivity was improved. According to the authors, insulin resistance may be closely related to the impairment in the mitochondrial ability to oxidize fatty acids, and IIT seems to revert that process [118].

Jeschke et al. also demonstrated that insulin has anti-inflammatory properties. It decreases pro-inflammatory cytokines and hepatic acute phase proteins, thus improving liver constitutive protein synthesis, and attenuating hypermetabolism after severe burns via alterations in the signaling cascade [119,120].

Gore et al. assessed the *in vivo* effects of hyperinsulinemia on human skeletal muscle in severely burned children. Patients with burns greater than 40% TBSA underwent metabolic evaluation, femoral artery and vein blood sampling and sequential muscle biopsies of the leg, before and after the infusion of insulin into the femoral artery. The authors created a local hyperinsulinemia with minimal systemic alterations, demonstrating that insulin has a direct effect on muscle protein synthesis in children with severe burn injury [121,122]. In a similar clinical experiment, Ferrando et al. showed that muscle anabolism could be achieved even at a submaximal insulin dose, thus minimizing the risk of hypoglycemia [123].

Numerous investigators have tried to establish an association between insulin treatment and a survival benefit, both in thermally injured children and adults. The literature agrees that the treatment with insulin decreases rates of infection, sepsis and organ failure, but analysis of data regarding mortality shows inconclusive results [124–127].

In the context of hypermetabolism secondary to severe burns, insulin seems to be an effective and safe anabolic agent for burn patients for several reasons: (1) it is less expensive than rhGH or IGF-1, (2) its side effect profile is well established and is limited primarily to hypoglycemia, (3) it seems to improve outcome by decreasing serum glucose levels and (4) it apparently enhances wound healing, both systemically and locally administered [128–132]. It is widely used in critically ill adult and pediatric patients that require glycemic control. From an anabolic perspective, the risk of causing hypoglycemia in a normoglycemic patient must be taken into consideration. Additionally, the insulin dose which can elicit anabolism and its organ protective effects is unknown and the ideal glucose target range remains unclear.

3.6. *Metformin*

Metformin has a dual mechanism of action in decreasing serum glucose levels. It both increases muscle glucose uptake and decreases hepatic glucose production. It suppresses hepatic glucagon and hence hyperglycemia by increasing the production of cyclic AMP. Metformin appears very well suited as a therapeutic agent as it can be administered *per os* during acute hospitalization. It is an antihyperglycemic agent that has rarely been associated with hypoglycemia. It is, however, contraindicated in hepatic and renal failure, due to increased risk of lactic acidosis [133–136].

Metformin has been demonstrated to augment muscle protein synthesis in the thermally injured. Hence, similar to insulin, it may have a role both as antihyperglycemic and anabolic agent for the critically ill population. Given its mechanism of action to increase insulin sensitivity, metformin and insulin may act synergistically to ameliorate glucose metabolism and halt the muscle catabolism induced by major burns [137,138].

According to Gore et al., although the mechanism by which metformin increases skeletal muscle protein synthesis is not entirely clear, there seems to be an association between high serum glucose levels and muscle protein breakdown. Therefore, the drug's anabolic effect may be related to its ability to ameliorate hyperglycemia [139]. Jeschke et al. recently

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demonstrated that metformin decreases serum glucose levels in burned patients as effectively as insulin with the additional benefit of a reduction in hypoglycemic episodes. Moreover, metformin has beneficial effects on fat metabolism and inflammatory response after thermal injury [140].

For its safety, efficacy and oral availability, it seems to be an anabolic agent that should be considered for patients who require glycemic control. However, it is a relatively novel agent in the arena of anabolism for burned patients and its entire side effect profile has yet to be determined. Currently, there are two ongoing clinical trials designed to help establishing the safety and efficacy of metformin, both in burned children and adults (NCT01666665 and NCT 01307306) [141,142].

3.7. *Thyroid hormones*

Critical illness and major trauma induce severe alterations in the hypothalamic–pituitary–thyroid axis which may compromise multiple metabolic functions. Growth, energy expenditure, cell turnover and cell respiration, among other functions, may be affected by this unbalanced and sudden change. These intricate and profound alterations have been referred as the "euthyroid sick syndrome", which should be distinguished from real hypothyroidism for accurate diagnosis and treatment [143].

There has been postulated that low serum thyroid hormone levels would be adaptive, a protective response to the hypermetabolism experienced by the critically ill. However, these patients show thyroid hormone levels inversely proportionate to biochemical markers of muscle and bone catabolism. Moreover, administration of exogenous thyroid hormones to such patients has been shown to reduce catabolic markers, which indicate that low thyroid hormone levels contribute to, rather than protect from, the hypermetabolism of the critically ill and the thermally injured [144].

Nonetheless, there is limited data on the indications for thyroid hormone replacement therapy to the thermally injured. Studies have shown that administration of T_3 to burn patients has no effect on the metabolic rate, serum catecholamine levels, or mortality from pneumonia or sepsis. These features indicate that the hypermetabolism experienced by burn patients is most likely secondary to an exaggerated sympathetic nervous system response rather than an unbalanced hypothalamic–pituitary–thyroid axis [145].

4. Conclusion

The metabolic repercussions of severe thermal injury can be devastated both acutely and in the long-term. Exaggerated inflammatory response, overstimulation of the sympathetic nervous system, hypercatabolism, insulin resistance and hyperglycemia are particular aspects of this syndrome that cause major consequences to the burned patients. Many pharmacological strategies have been tried to ameliorate this condition, either by antagonizing the β-adrenoreceptor stimulus (anticatabolism) or reversing the negative net protein balance (anabolism).

Most of the drugs tested for research purposes are not yet established clinical therapies in spite of their potential benefit. Propranolol and oxandrolone have shown great promise but are not yet considered to be standard-of-care therapy.

Propranolol may be an effective adjunct to decrease thermal injury catabolism in pediatric patients. It has been shown to decrease cardiac work, REE, and lipolysis. It has also been demonstrated to increase skeletal muscle synthesis, reversing the catabolic shift induced by severe burns. Further evidence in adult and elderly burned patients is still needed to clarify its potential use for all thermally injured populations.

Treatment with oxandrolone during the acute phase of burn injuries does not affect mortality or risk of infection, but it has been demonstrated to shorten length of hospital stay, skin graft donor-site healing time, time between surgical procedures and weight and nitrogen loss. It is also beneficial during the rehabilitation phase, showing shortened length of hospital stay, decreased weight loss, and gain in lean body mass at 6 and 12 months postburn. Moreover, the drug is orally available, has a tolerable adverse effects profile, and is effective for both children and adults.

Further research efforts should focus on the understanding of the synergistic effects of the association of propranolol and oxandrolone. The combination of effective sympathetic nervous system antagonism and positive net protein balance may be the cornerstone of the treatment for the burn-induced hypermetabolic syndrome.

Conflict of interest

EG and SS declare no competing interests. MJ received grants from National Institutes of Health, Canadian Institutes of Health Research and CFI Leaders Opportunity Fund. None of the authors had any type of financial gain or relationship to pharmaceutical companies.

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