

Review

Current understanding of the chronic stress response to burn injury from human studies

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Abstract

There is a marked inflammatory and hypermetabolic response following a burn injury. The inter-linked responses are more pronounced than for other forms of trauma and can persist for ≥ 3 years post-injury in burned patients. After a burn, patients have an increased risk of diseases of ageing including cancer, diabetes and cardiovascular disease, highlighting the need for effective long-term strategies to ameliorate the stress response post-burn. Current therapeutic strategies for post-burn recovery include removal of damaged tissue with surgical excision and wound repair, nutritional supplementation and rehabilitative exercise. These strategies aim to minimize the hypermetabolic and inflammatory responses, as well as reducing the loss of lean body mass. This review briefly summarises the inflammatory and hypermetabolic responses and provides an update on the current therapeutic strategies for burned patients. The review examines the persistent nutritional challenge of ensuring sufficient energy intake of each macronutrient to fuel the hypermetabolic and counteract the catabolic response of burn injury, whilst reducing periods of hyperglycaemia and hypertriglyceridemia. Patients require individualized treatment options tailored to unique systemic responses following a burn, facilitated by a precision medicine approach to improve clinical and physiological outcomes in burned patients. Thus, this review discusses the utility of metabolic flexibility assessment to aid clinical decision making and prescription relating to nutritional supplementation and rehabilitative exercise in the burned patient.

Key words: Burns, Metabolism, Inflammation, Metabolic flexibility, Exercise, Nutrition, Clinical care

Highlights

- The systemic response following a burn is still challenging for clinicians in post-injury care.
- Metabolic flexibility has yet to be investigated in the burned population.
- New assessment methods may allow for a precision medicine approach to long-term treatment.

Background

Burns result from exposure to flame or the ignition of flammable objects, as well as chemical, electrical burns and scalds due to heated liquids and oils [1]. Despite significant advances in treatment and management of burn injury, the complex physiological responses to a burn injury remain a challenge for optimal care. In Australia, ~1% of the population sustains a burn each year, half of these are severe enough to affect daily life [2,3]. Within 3 years of severe burn injury, 24% of patients report a post-injury complication and 8% of patients have died [4,5]. A complex physiological response ensues, characterized by an acute (24–48 h post-burn) hyperinflammatory and hypermetabolic period, which remains elevated for at least 1–3 years after injury, depending on burn severity [6,7]. This heightened inflammatory and metabolic response may be associated with long-term morbidity in patients with burn injuries, leading to increased incidence of diseases of ageing, including cancer [8], type 2 diabetes (T2D) [9,10], cardiovascular and a host of other systemic diseases [5,7,11–25]. This review describes the inflammatory and metabolic responses to a burn injury and provides insight on current non-medication-based lifestyle interventions used within clinical care, as well as a novel point-of-care application of metabolic assessment.

Search strategy

A computer-based search of PubMed was conducted for all relevant articles published before 2022. The following search terms and Boolean operators were used: (burns OR burn injury) AND (metabolism OR indirect calorimetry OR metabolic flexibility) AND (inflammation OR inflammatory cytokines). The search was limited to publications in English, due to the authors' lack of proficiency in languages other than English.

For studies to be included, titles and abstracts were screened by the first author (TO) to ensure they met the following criteria: (1) were conducted on humans (no animal or *in vitro* studies were reviewed); and (2) examined the relationship between burn injuries and measures of inflammatory cytokines or metabolism by means of indirect calorimetry. Articles were excluded if they: (1) were a conference proceeding abstract only; (2) were a review or theoretical article; or (3) were non-peer reviewed or a book chapter. Additional relevant articles, including those undertaking mechanistic work, are referred to throughout this manuscript based on supplementary bibliography searches (Figure 1).

Review

With the constant evolution of medical technology and knowledge, it is paramount to optimize clinical care for patients by utilizing novel point-of-care assessments to develop an understanding of the real-time interaction between metabolic and inflammatory responses, such as

metabolic flexibility (MetF). In doing so clinicians will be able to further their current understanding of ameliorating post-burn physiological stress throughout various stages of recovery.

Inflammatory response

The localized inflammation that occurs as a result of a burn injury is typified by the tissue response in the zone of stasis [26]. This zone is characterized by vascular dysfunction resulting in low levels of perfusion and an excessive inflammatory response [27]. One of the cellular mechanisms that emerges in the acute post-burn inflammatory response is the chronic activation of mast cells [26]. These ubiquitous cells store and produce a multitude of mediators, including pro- and anti-inflammatory cytokines once activated [11,28,29].

While mast cells play important roles in tissue repair and wound healing initially, chronic stimulation or over-activation can be detrimental, specifically in fibrotic processes of the skin that lead to scarring and hypertrophy of scars [11,30–32]. The degranulation of mast cells has been shown in animal models to be a virtually instantaneous response that leads to enhanced oxidative stress and production of reactive oxygen species, which underpins the hypermetabolic response post-burn [26,33]. This occurs through various cellular mechanisms, including hypoxia in healing tissues due to reduced blood flow associated with thrombosis of vessels, upregulation of inflammatory markers and proapoptotic factors. The oxidative stress rapidly depletes tissue adenosine triphosphate (ATP), leading to an increase in adenosine monophosphate which can be further converted into adenosine and hypoxanthine; the latter being a substrate for xanthine oxidase which can amplify free radical production [34].

Free radicals have been found to damage mast cell membranes [35], which may further stimulate the mast cell proinflammatory cytokine release in the post-burn phase. The increased level of free radical production post-burn has been implicated in inflammation, immunosuppression, metabolic response, infection, sepsis, tissue damage and multiple organ failure [36].

Acutely, the damage sustained during a burn injury initiates an early (<12 h) inflammatory response, characterized by an increase in interleukins 10 (IL-10), IL-1a and latency-associated peptide, followed by a subsequent (36–48 h) peak in IL-6, IL-8 and monocyte chemotactic protein 1 [4,37–41]. The burn area is positively related to the severity of injury and therefore so too are these markers and the cytokines released [38,39,42,43]. Total body surface area (TBSA) burned appears to be most strongly correlated with increases in IL-8, IL-10 and granulocyte-colony stimulating factor (G-CSF), representing increased anti- and pro-inflammatory stimulation, while the relationship between burn size and tumour necrosis factor alpha (TNF- α) is less clear [39,42,44,45].

Although the release of pro-inflammatory cytokines IL-6, IL-8 and TNF- α is expected to precede the increase in anti-inflammatory cytokines, such as IL-2, IL-4, IL-10 and G-CSF,

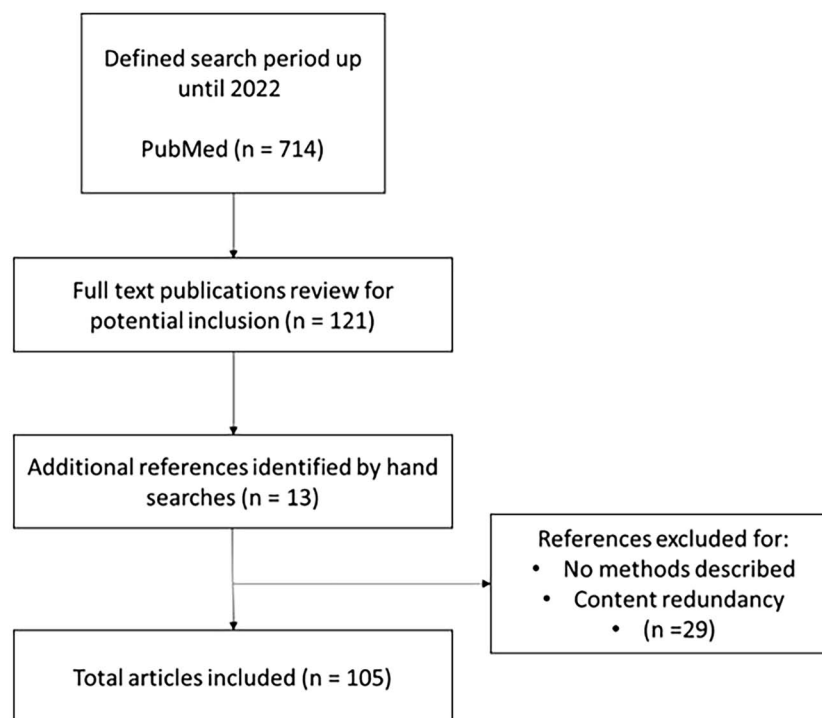


Figure 1. Literature review flowchart

this pattern does not appear consistently [37,39,42,44,46,47]. This may be due to the site and tissues affected by the burn, the timing of the blood sampling (hours post-burn; diurnal testing times) described in the research or the pathophysiological magnitude of the cytokine response. At 24 h post-injury, IL-10 appears to be higher in survivors compared to non-survivors [38], while 4–7 days after severe burn injury, concentrations of circulating IL-4, IL-6, IL-8 and G-CSF appear higher in survivors compared to non-survivors. These results suggest surviving burns patients have a higher capacity to counterbalance the initial pro-inflammatory response, which is energetically demanding and complex [48–50]. Adenosine, which increases in concentration in response to increased rates of ATP metabolism, may also play a role due to its cytokine-producing effect [43,51]. Concentrations of inflammatory cytokines remain above those in non-burned patients for at least 20 days post-injury, however the specific spectrum and concentration of these cytokines are still unclear [38,52,53] and they have been reported to persist at elevated levels after 3 years post-injury in paediatric patients [5,54]. The excessive free radical production post-burn likely contributes to the varied spectrum and concentration of cytokine expression, as the hypermetabolic response leads to upregulation of inflammatory cytokines [26].

Further indication of the ongoing inflammatory insult after burn is confirmed by clinical studies describing active hypertrophic scar changes many years to decades after burn injury [16,23,55–58]. Previous research has indicated that mast cell over-activation post-burn is linked to the fibrotic processes of scarring and hypertrophy of scars [30,33],

suggesting that the ongoing systemic inflammatory challenge brought about by upregulated inflammatory markers and free radical production in the body after non- and severe burn injuries is associated with a broad spectrum of latent disease sequelae identified in multiple population health and big data studies, which may allow for a prognostic application of cytokine expression in burned patients [8–10,12–15,17,18,40,41,59,60].

Metabolic stress

The hypermetabolic response to burn injury is associated with chronic adrenergic stimulation [61,62], resulting in resting energy expenditure (REE) of 40–80% above age-predicted levels, and is characterized by excessive substrate cycling [6,62,63]. This chronic adrenergic stimulation brought about by catecholamine and cortisol release in the body increases the likelihood of long-term morbidity for developing diseases of ageing [11,64,65]. Approximately 57% of the hypermetabolic response to burns injury is related to ATP-dependent processes, including increased protein synthesis, hepatic gluconeogenesis, as well as glucose and fatty-acid cycling [6]. The additional ~40% increase is understood to be due to mitochondrial uncoupling [6], particularly in brown adipose tissue as a result of adrenergic activation, wherein oxygen uptake is increased to account for the reduced phosphate/oxygen ratio in mitochondrial ATP synthesis [6].

MetF is a concept relating to the ability of the body to adapt or respond to dependent changes in metabolic or energy demand [66]. This concept has been promoted in the context of switching fuel utilization between fatty acids in

a fasted state to an upregulated glucose oxidation pattern during the fed state. This switch in fuel utilization requires a complex interplay between lipid and glucose oxidation, which is mediated via both intracellular changes in metabolite concentrations and via systemic endocrine changes. One mechanism that has been proposed is the disturbance to skeletal muscle lipid metabolism [67], with diabetic patients having an imbalance between fatty acid uptake and oxidation which enhances the accumulation of ceramides and triglycerides in the skeletal muscle [68], the accumulation of which may interfere with insulin signalling [69]. It was found that in obese and T2D patients, fat oxidation was reduced at fasting, and was less suppressed compared to healthy populations after feeding [70]. In addition, the uptake of free fatty acids into the skeletal muscle during fasting in diabetic patients increased, while the fatty acid uptake was impaired after feeding [70,71].

Burn-injured patients experience rapid and significant reductions in mitochondrial function [62], excessive and futile substrate cycling [61] and reduced skeletal muscle mass [72,73]. Consequently, burned patients have an increased incidence of insulin resistance in the short- to medium-term and a high prevalence of T2D in the longer-term [7,74,75]. T2D is characterized by poor MetF, which refers to the ability of the body to adapt fuel systems to supply energy requirements as per conditional demand [66]. Given the pathognomonic similarities between T2D and burn injuries of altered substrate cycling, insulin resistance and impaired cellular function, it is proposed that the changes to MetF seen in T2D will also be observed in burn-injured patients.

Assessment of MetF in burned patients

Poor MetF can be identified as a sluggish response in adjusting energy utilization to changes in energy requirements (Figure 2). MetF was originally described by Randle *et al.* (1963) as a principle to explain elevated fatty acid oxidation and diminished glucose oxidation in T2D [76]. Subsequent studies investigating glucose and fatty acid metabolism mechanics utilized an *in vivo* limb arteriovenous balance technique to demonstrate poor MetF in T2D and obesity, to obtain measures of leg muscle glucose uptake, glucose oxidation and glycolysis, which revealed that post-absorption where lipid utilization should again predominate, skeletal muscle in individuals with T2D and obesity persisted with glucose oxidation after the metabolic stimulus [71,77,78]. Due to the challenges of *in vivo* limb-balance studies, we propose adopting standard clinical indirect calorimetry assessments [79] in a new model to provide a measure of MetF. This would be achieved following a 15 min baseline resting-energy expenditure assessment, as per best practice guidelines established by Compther *et al.* [80] to determine the resting respiratory exchange ratio (RER) values in the burned population, followed by the introduction of a metabolic stimulus such as energy intake or exercise, after which a 60 min

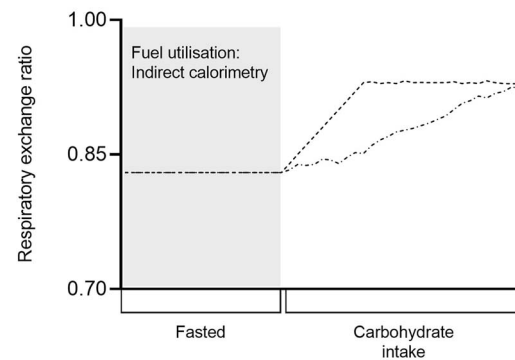


Figure 2. Depiction of metabolic flexibility measured using indirect calorimetry. During fasting conditions, lipids are the major fuel source to support metabolism. Oxidation of lipids results in a RER [measured as volume of carbon dioxide/ volume of oxygen (VCO_2/VO_2)] value close to 0.70. Ingestion of carbohydrate increases blood glucose supply, resulting in a shift towards utilization of glucose as the primary fuel source. Oxidation of glucose results in an RER value of 1.00. In an inflexible metabolic system, the transition from primarily lipid oxidation to glucose oxidation is not as rapidly sensitive, as depicted in the figure. RER respiratory exchange ratio

indirect calorimetry assessment of REE and RER is conducted as shown in Figure 2 [66].

Metabolic inflexibility is characteristic in individuals with T2D and is linked with mitochondrial dysfunction [66], which is also a common diagnosis during the acute burn period. The risk of metabolic inflexibility in burned patients is increased in the persistent and chronic adrenergic activity and pro-inflammatory environment, which while present in T2D [70,71,77,78], has a greater impact within burn-injured patients. Interventions to facilitate MetF may be useful in individually tailoring nutritional support and rehabilitative programmes, as well as identifying individuals at increased risk of longer-term complications such as T2D.

Musculoskeletal catabolism

Despite increases in skeletal muscle protein synthesis following burn injury, protein degradation exceeds the rate of synthesis, resulting in net skeletal muscle catabolism [73]. This is thought to be due to the inflammatory and protein catabolism response following a burn injury [73,81]. As decreases in lean body mass are associated with increased morbidity, and in some cases mortality in burned patients [72], increased skeletal muscle catabolism is a major concern in the context of long-term outcomes. Specifically, as loss of lean body mass increases, so does the likelihood of mortality following a severe burn injury, with $\geq 40\%$ loss of lean body mass representing a 100% mortality rate [72]. Using an *in vitro* cell culture model, Pin *et al.* [82] identified circulating transforming growth factor β as a potential candidate for inducing muscle atrophy via the protein kinase B/mammalian target of rapamycin (AKT/mTOR) signalling pathway. While skeletal muscle mass loss may not be considered a primary concern in non-severe burns, loss of muscular function needs to be considered as does the associated physical activity reduction

and morbidity, as a result of hypermetabolism and the inflammatory response. Despite the majority of skeletal muscle catabolism research being reported in severe burns, preliminary research in non-severe burns has demonstrated similar physiological trends to those reported in major burns [83]. This increased protein catabolism is attributed to increased oxidation of proteins essential to homeostatic function to meet the demands of the hypermetabolic response in the days, weeks and even years following a burn injury [84]. This may result in long-term compromise to the function of skeletal muscle architecture and cellular membrane integrity [5,85].

Another notable effect of a burn injury on the musculoskeletal system is its effects on bone mineral density. This occurs through the acute resorption of bone, likely caused by the release of cytokines IL-1B and IL-6, that extricates calcium, phosphorus and magnesium [86,87]. All of this has been previously linked to the post-burn inflammatory response and hyper-metabolism [82,86].

Current therapies to ameliorate hypermetabolic responses

Surgical intervention In all but trivial injuries, the skin loses the capacity to heal by regeneration. Conservative wound care is associated with significant delays in healing which is associated with poor scar outcome with increased risk of morbidity and mortality primarily due to infection [88]. Surgical intervention is focused on removal of the necrotic tissue and repair of the resulting wound. The capacity to undertake surgery for major burn injuries has been made possible by a combination of improved critical care and tissue engineering approaches to augment traditional skin-grafting techniques [3].

The surgical excision of the burn wound reduces the ongoing sources of inflammation in all burn injuries [89]. In burns $\geq 50\%$ total body surface area, surgery is associated with a 40% reduction in REE when excision of dead tissue and coverage is achieved within 3 days of injury, compared to patients with similar size burns undergoing their procedure within 7 days [89]. Importantly, surgical excision was associated with reduced rates of sepsis observed amongst patients who received surgery within 3 days of injury (20% *vs* 50% in the late-excision group) [89]. Through surgical intervention, the hypermetabolic state is partially attenuated and is associated with a decrease in muscle protein catabolism and REE [90]. The removal of dead tissue is considered a primary means of reducing the ongoing stress response following a burn [89,91].

However, the majority of burn injuries treated with acute surgery are not major, or classified as $>20\%$ TBSA, with the most recent Burns Registry of Australia and New Zealand report identifying that 92.4% of adult cases affected $\leq 20\%$ TBSA, with 76% of all cases requiring at least one surgical procedure [92]. The technique and timing of surgical intervention in these burn injuries is much debated. The key factors influencing surgical decision-making are traditionally

%TBSA, depth of the injury, body site and age of the patient [93]. The impact of the burn systemically in the non-severe injury presents an opportunity to explore the influence of these factors on inflammation with reduced confounding compared to major burns. Investigating the impact of surgery on MetF in a significant proportion of non-severe burns can assist in defining optimal treatment timing. In an inflammatory metabolic response context, surgery could be viewed as a secondary traumatic event after burn. Surgical stress is an additional acute response to one or more breaches of the body's barrier involved in the surgical process, including sterile incision/excision, pathogen invasion and/or anaesthesia, and can affect whole body homeostasis [94]. This warrants further investigation to understand the role of surgery in the inflammatory and metabolic response after the acute initial injury, and whether on balance between the stress of the surgery and the stress of leaving dead tissue *in situ*, it increases or decreases systemic stress post-burn. This will facilitate an improved clinical understanding of the potential contribution of interventions to inflammatory and hypermetabolic responses to optimize recovery for the majority of patients sustaining burn injuries [95–97].

Nutritional support MetF assessment will provide insight into how patients are utilizing macronutrients throughout key periods of the day and in response to specific treatments and/or recovery events, allowing an opportunity to enhance nutritional prescription beyond current clinical guidelines.

Nutritional support for burned patients plays an important role in addressing and manipulating excessive energy expenditure due to hypermetabolism, as well as matching specific macronutrient utilization to minimize loss of lean body mass [61,98,99]. The caloric requirements for burned patients are 20–40% higher than normal predictive equations [83,98]. For this reason, specific equations have been developed [100,101], such as the Toronto formula, which was found to be accurate in measuring excessive energy use in burns ($r^2 = 0.67$) taking into consideration total body surface area burned, caloric intake, body temperature and days post-burn [102]. However, results suggest that one-third of energy expenditure in burned patients remains unexplained [83]. These equations should be used as a guide, in conjunction with other methods such as indirect calorimetry [103].

Immediately following a burn injury, increased adrenergic activity leads to systemic lipolysis, resulting in increased circulating lipid concentrations [98], which is an important consideration of burns, in that these patients are not active prior to surgery and for the duration of their hospital stay due to wound closure surgeries. However, only 30% of free fatty acids are metabolized in energy yielding pathways, with the remainder accumulating in the liver and undergoing re-esterification, potentially contributing to non-alcoholic fatty liver disease, liver cirrhosis and liver failure [98], and further increasing the likelihood of systemic morbidity after burn injury [98]. Appropriate supplementation of fats, suggested

to be 0.5–1 g fat/kg/day in the post-burn diet can prevent fatty acid deficiency, whilst also avoiding excessive free fatty acids that can be esterified in the liver, thus ameliorating futile lipolysis [98]. Phospholipids including *trans* fatty acids and saturated fatty acids have been associated with increased levels of C-serum reactive protein (CRP) and TNF- α in non-injured populations, suggesting a link between fat ingestion and inflammation throughout the body [104,105]. Given the varied and excessive cytokine expression after burn injury, developing a deeper understanding of the anti-inflammatory effect of fats on burn injured patients' inflammatory status will supply the scientific evidence to prescribe an interventional dietary intake for patients and provide an opportunity to improve physiological and functional outcomes post-burn [26].

Conversely, the rate of glucose utilization in burned patients can exceed 7 g/kg/day [98]. Glucose is universally used throughout the immune system, particularly by the white blood cells, stimulating fibroblast growth and collagen production [106]. Careful supplementation is needed when prescribing carbohydrates, which are usually prescribed for a long duration at low volume due to the ongoing need to utilize glucose. Inadequate carbohydrate availability may lead to uncontrolled protein catabolism, while excessive levels of carbohydrate can lead to hyperglycaemia, dehydration and respiratory issues [98]. This is made more complicated by increased gluconeogenesis and hepatic glycolysis in response to the adrenergic activity after burn [107], as well as reduced sensitivity of skeletal muscle to insulin as a result of increased plasma free fatty acids [108]. Pittas *et al.* identified that non-injured overweight patients with a diet consisting of a low glycaemic load had significantly lower levels of CRP compared to non-injured overweight individuals on a high glycaemic load, suggesting that manipulation of carbohydrate quality (high *vs* low glycaemic load) could impact other inflammatory markers [105,109].

Protein oxidation, or degradation, can be 50% higher in patients after burn, relative to non-burn patients, and therefore protein supplementation to counter this response via increased amino acid availability and protein synthesis stimulation is critical [98]. Some amino acids, such as glutamine, have been identified to modulate the metabolism and immune system and may play a role in impacting hypermetabolic states [110,111]; however, whether the amino acid composition in the period after burn injury is important requires further investigation.

With advancements in technology and assessment techniques, along with the accumulating understanding of appropriate caloric balance, macronutrient supplementation and timing of feeding should allow a more individualized and scientific approach to clinical nutritional prescription for patients with burn injuries, rather than relying upon predictive equations utilizing anthropometric measures alone. MetF assessment will allow for individualized nutritional intervention and exercise prescription in burned patients, in a move towards more individualized and patient-specific

programming [112]. Specifically, if MetF is compromised in an individual, the macronutrient content of meals can be controlled to minimize the sudden shift in substrate oxidation. For example, the long-established second-meal phenomenon describes how the glycaemic response to a meal is diminished when the meal is preceded by energy intake in a prior meal [113]. From a practical perspective, this would support a low glycaemic load to be ingested at the first meal (i.e. breakfast) to ensure a gradual shift in substrate oxidation from systemic fat oxidation (due to the short-term overnight fast; ≥ 8 h) to the postprandial period, rather than a high glycaemic-load breakfast. The glycaemic load at subsequent meals may then be increased if needed, given that the glycaemic response to the second meal is diminished [67]. The optimal timing of meal intake and proportional macronutrient prescription has yet to be found, but further investigation may provide clarity on how specific feeding doses and timing can help modulate substrate uptake and oxidation [67]. There has been no previous research investigating MetF assessment within burned populations to the authors' knowledge.

Exercise Both cardiovascular and resistance-based exercise training have been shown to improve clinical and functional outcomes in patients with burns. Most notably, changes were observed in the preservation of lean body mass and an increase in skeletal muscle synthesis [112,114–116]. It is important to note however that most research in exercise post burn has been in paediatric cases [117,118], with a recent systematic review examining resistance training for rehabilitation after burn injury highlighting that 81% of included studies included paediatric patients only [112]. This positive response to exercise in burns patients is unsurprising, given the multi-organ and system response associated with exercise in the non-burned population, which sees favourable alterations in the inflammatory, metabolic and musculoskeletal systems [119]. In healthy and clinical populations, exercise is associated with increased lean body mass and muscular strength [120], skeletal muscle glycogen storage capacity [121], skeletal muscle oxidative capacity and pulmonary function [122], insulin sensitivity [123], anti-inflammatory activity [124] and improved liver function [125].

A challenge in prescribing exercise for patients with burns is achieving the appropriate balance in the volume of resistance-based and cardiorespiratory-based exercise, so as not to exacerbate aerobic-exercise-induced cortisol release. A further challenge is the timing of the exercise programme during the recovery phase following burn injury to optimize the benefits of exercise training, however time to commencing rehabilitation post-burn has not been investigated thus far [112]. Most commonly, exercise programmes have been delivered to burned patients 6 months post-injury for 12 weeks duration [116,126], however studies have indicated that commencing exercise as early as 72 h post-burn can further minimize lean body mass loss [127,128]. Resistance training, commenced as an acute form of rehabilitation for burned patients, was importantly found to be not harmful to

patients, but also led to improvements in functional outcomes and rate of recovery, as well ameliorating peak and faster rate of reduction in CRP, compared to a control group completing standard treatment post-burn [127].

A primary consideration for prescribing exercise in burned patients is to avoid acutely exacerbating hypermetabolism and skeletal muscle catabolism resulting from increased circulating cortisol levels, as this may contribute to the burn-injury-induced stress response, potentially leading to further complications with post-burn morbidity [129,130]. This cortisol rise was demonstrated in a non-injured population by Hill *et al.*, who reported that cortisol increased up to 83% in an extended bout of aerobic exercise (≥ 20 min) at an intensity of 80% of volume of inspired oxygen (VO_2) max, while aerobic exercise at an intensity of 40% only saw a slight increase to cortisol levels 5.6% above resting values [129]. This may be attributed to daily variation in cortisol levels, warranting further investigation. Given a primary consideration for exercise prescription in burned population is avoiding hypermetabolism and skeletal muscle catabolism, it is plausible that a more appropriate exercise prescription would be a primary focus on resistance training with minimal focus on cardiovascular activity, with aerobic exercise intensity not exceeding 60–80% of VO_2 max [129,131].

Exercise itself requires a sudden shift in energetics, as it can increase energy expenditure 25-fold [66]. This increased energy expenditure is fuelled by increased utilization of both intramuscular substrates (glycogen, triglycerides, amino acids) and delivery of systemic substrates (plasma glucose, free-fatty acids), with substrate utilization being highly intensity- and duration-dependent. Thus exercise improves metabolic flexibility by training the system to effectively and rapidly switch between energy sources [132]. During exercise, substrate uptake into skeletal muscle is driven by a coordinated increase in capillary perfusion, increased surface membrane transport capacity and intracellular substrate flux [133], allowing the skeletal muscle cells to increase their uptake of circulating glucose and fatty acids required for the increased energy demand brought about by exercise.

Future implications

Pereira *et al.* described a paradigm shift within burns treatment focusing on quality of life and survivability post-burn injury, rather than treatments focusing on simply preventing death [134]. Since then, numerous studies have investigated the role of exercise and nutrition within burns rehabilitation [112,114,116,128], focusing on quality of life and survivability in the burned population.

There is a number of inflammatory marker targets yet to be investigated for their involvement in or impact on MetF relating to the current interventions being used to manage both the hypermetabolic and inflammatory response post-burn injury.

The development of new point-of-care assessment techniques will be crucial in understanding the timing of when patients shift between fuel substrates in the chronic phase of

the burn injury response. These assessment techniques will play a pivotal role in the development of effective real-time prescription of nutrition and exercise plans to reduce the long-term burden of a burn injury [11]. By developing patient-specific treatment plans based upon individual responses to nutritional and exercise-based therapies, clinical research can work towards developing effective strategies to mitigate these deleterious responses. This would facilitate another step towards a precision-medicine approach to managing burn trauma.

Conclusions

By utilizing novel approaches, such as those focused on MetF, to assess the stress response following a burn injury, clinicians will have a unique opportunity to individualize nutritional and rehabilitative exercise prescription to adopt a precision medicine approach to lifestyle-based intervention post-burn injury in order to counteract the unparalleled systemic stress.

Abbreviations

ATP: Adenosine triphosphate; G-CSF: Granulocyte-colony stimulating factor; IL-10: Interleukin 10; MetF: Metabolic flexibility; REE: Resting energy expenditure; TBSA: Total body surface area; T2D: Type 2 diabetes; $\text{TNF-}\alpha$: Tumour necrosis factor alpha.

Authors' contributions

The conceptualization of this manuscript involved all authors. The literature search and original draft was written by TO, with review and editing from BW, TF, DWE and FW.

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Conflict of interest

None declared.

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