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Research Article

Current understanding of thermo(dys)regulation in severe burn injury and the pathophysiological influence of hypermetabolism, adrenergic stress and hypothalamic regulation—a systematic review

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Abstract

Background: In this systematic review, we summarize the aetiology as well as the current knowledge regarding thermo(dys)regulation and hypothermia after severe burn trauma and aim to present key concepts of pathophysiology and treatment options. Severe burn injuries with >20% total body surface area (TBSA) affected commonly leave the patient requiring several surgical procedures, prolonged hospital stays and cause substantial changes to body composition and metabolism in the acute and long-term phase. Particularly in severely burned patients, the loss of intact skin and the dysregulation of peripheral and central thermoregulatory processes may lead to substantial complications.

Methods: A systematic and protocol-based search for suitable publications was conducted following the PRISMA guidelines. Articles were screened and included if deemed eligible. This encompasses animal-based *in vivo* studies as well as clinical studies examining the control-loops of thermoregulation and metabolic stability within burn patients

Results: Both experimental animal studies and clinical studies examining thermoregulation and metabolic functions within burn patients have produced a general understanding of core concepts which are, nonetheless, lacking in detail. We describe the wide range of pathophysiological alterations observed after severe burn trauma and highlight the association between thermoregulation and hypermetabolism as well as the interactions between nearly all organ systems. Lastly, the current clinical standards of mitigating the negative effects of thermodysregulation and hypothermia are summarized, as a comprehensive understanding and implementation of the key concepts is critical for patient survival and long-term well-being.

Conclusions: The available *in vivo* animal models have provided many insights into the interwoven pathophysiology of severe burn injury, especially concerning thermoregulation. We offer an outlook on concepts of altered central thermoregulation from non-burn research as potential areas of future research interest and aim to provide an overview of the clinical implications of temperature management in burn patients.

Key words: Animal model, Burn shock, Hypothermia, Thermoregulation, Temperature management, Burn injury, Hypermetabolism

Highlights

- This article examines the connection between thermoregulatory processes in different organ systems in patients with severe burn injuries.
- This study further connects principles of dealing with thermoregulatory problems in burn patients with basic science and animal-based research approaches examining underlying mechanisms.

Background

Severe burn injuries, encompassing more than one-fifth of total body surface area (TBSA) remain a substantial source of worldwide morbidity and mortality, with up to 300,000 deaths per 11 million incidences per year by WHO estimates [1–3]. Although incidences of burn trauma have declined gradually, burn injury remains the fourth most common type of trauma worldwide [2]. It affects younger patients in a bimodal distribution, with the majority of cases in children (1–15.9 years) and those of working age (20–59 years) [4]. Several decades of research have led to a systemic understanding of burn injury. In addition to the obviously catastrophic damage to the skin, in its acute phase, severe burn trauma is known to cause a systemic state of hyperinflammation, hypercatabolism with severe wasting of skeletal muscle, metabolic disbalance, adrenergic overstimulation, severe immunosuppression with increased susceptibility to infection and sepsis, and multiple organ failure [5,6]. Despite substantial efforts being made, disturbed thermoregulation represents a nodal hub in the systemic concept of burn injury. In this review, we summarize current knowledge regarding the physiology of thermoregulation and thermodysregulation. In order to gain a more profound understanding of the pathophysiological background, we review experimental models that assess changes in thermoregulation on various systemic levels in the setting of burn injuries. We provide an overview of the consequences and clinical effects of thermodysregulation and therapeutic concepts in severely burned patients. Lastly, we summarise clinical practices in the treatment of burn-related changes in body-temperature and metabolic derangement, assess the impact of hypermetabolic, hyperinflammatory and adrenergic stimulatory alterations on thermoregulation and provide an outlook on potential areas of interest for further research.

Methods

For this systematic review, we conducted a systematic and protocol-based search for suitable publications according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed, Google Scholar and Cochrane were searched until January 2022 for medical literature published since 1970 in English, French, Spanish and German using synonyms of the following keywords 'temperature', 'thermoregulation', 'burn patient', 'heat loss', 'burn injury', 'hypothermia', 'hypermetabolism', 'sheep', 'pig', 'mouse' and 'rat'. All types of publications were included if they described an animal burn-model, addressed prehospital, acute or long-term treatment as well as further implications of burn injury, or focused on experimentally uncovering molecular mechanisms of thermodysregulation following burn injury. To attain additional studies, the bibliographies of retrieved articles were screened for relevant articles. First, publications were screened via abstract and if deemed eligible were further analysed regarding areas of interest such as metabolism and thermoregulation, as well as basic science studies researching underlying molecular patterns. In accordance with the PRISMA guidelines, a flowchart highlighting the inclusion/exclusion criteria and search strategy is provided in Figure 1.

The database search resulted in 556 articles, one of which was removed as a duplicate. Including 75 articles obtained after review of references and two more being removed as a duplicate, 628 records were screened. After exclusion of 541 articles, 87 records were included in the systemativ review. A diagram detailing this process is shown in Figure 1.

Results

Humans require a relatively stable body temperature of around 37–38°C to maintain normal metabolic function. The thermoregulatory system located in the preoptic anterior hypothalamus (POAH) is closely connected to afferent signals originating in heat and cold receptors in the skin surface, deep abdominal and thoracic tissues, spinal cord and other portions of the brain [7,8]. Thermosensory neurons transmit these afferent signals through e.g. the spinothalamocortical tract. When the core temperature falls below or rises above the threshold temperature, behavioural and autonomic responses are set in motion to return the temperature to its normal state, the so called setpoint temperature. The skin with its underlying fat and muscle tissue not only functions as a barrier against infectious particles and the external environment [9] but also serves as a complex functional
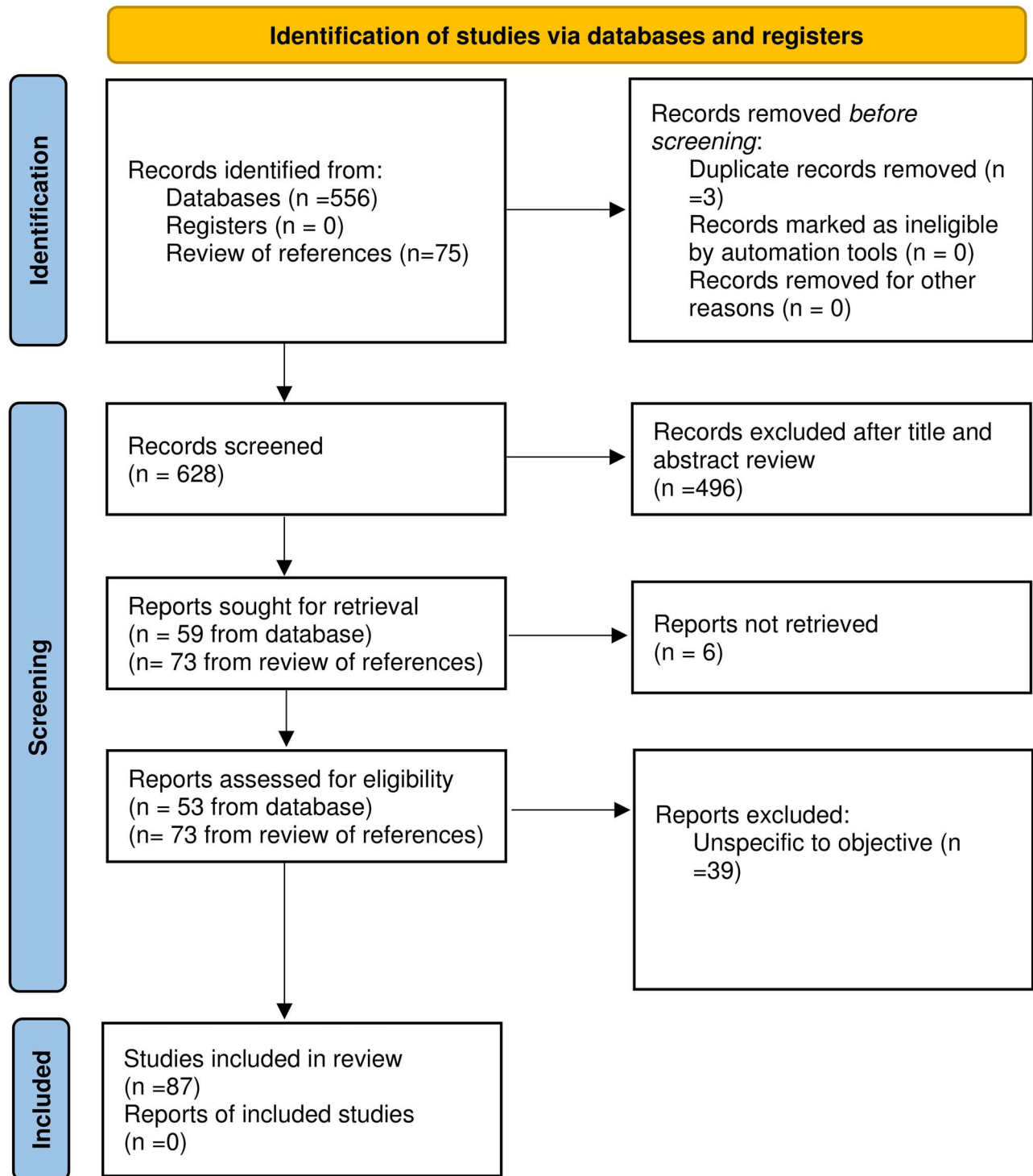
Identification of studies via databases and registers

Identification

Records identified from:
Databases (n =556)
Registers (n = 0)
Review of references (n=75)

→

Records removed *before screening*:
Duplicate records removed (n =3)
Records marked as ineligible by automation tools (n = 0)
Records removed for other reasons (n = 0)

Screening

Records screened
(n = 628)

→

Records excluded after title and abstract review
(n =496)

Reports sought for retrieval
(n = 59 from database)
(n= 73 from review of references)

→

Reports not retrieved
(n = 6)

Reports assessed for eligibility
(n = 53 from database)
(n= 73 from review of references)

→

Reports excluded:
Unspecific to objective (n =39)

Included

Studies included in review
(n =87)
Reports of included studies
(n =0)

Figure 1. PRISMA flowchart highlighting inclusion and exclusion criteria and search strategies

structure to regulate the body's core-temperature within its normal range. When placed in a cold environment, a healthy human's response comprises of muscle contractions, which accumulate to shivering, constriction of (sub)cutaneous blood vessels, which minimize heat loss, and behavioural changes [10]. When temperatures drop further, the body's metabolism increases. In burn patients, however, the overall metabolism is already increased even in thermoneutral and warm environments and their skin and body temperature is higher than normal. This phenomenon is part of the systemic response of catabolic hypermetabolism which is further aggravated when placed in a cold environment, resulting in a strong increase in metabolism [11,12]. These regulatory mechanisms are crucial in preserving a normal
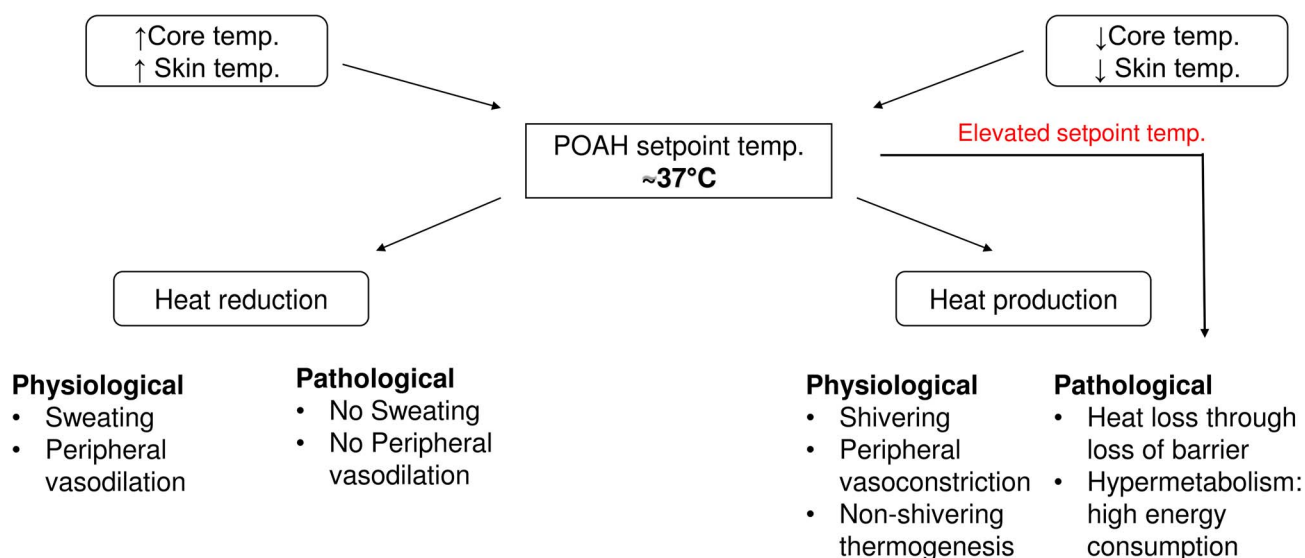
Figure 2. Summary of the core principles of physiological and pathological thermoregulation, *POAH* preoptic anterior hypothalamus

body temperature under different conditions. In the case of severe brain injury however, direct damage to brain regions as well as metabolic derangements, together with inflammatory processes and immense catecholaminergic overstimulation, can lead to altered thermoregulation and dysfunction, causing e.g. elevated temperatures in the early stages after the injury [13]. Also, infections and sepsis can lead to elevated body temperatures, namely fever, that is in turn caused by a variety of inflammatory mediators. The aforementioned knowledge of thermoregulation (e.g. via changes in autonomic regulation) has been available for some time now, although central thermoregulatory processes and their underlying molecular patterns are far less well understood. Also, not much is known about interoceptive temperature receptors that are located inside organs and body cavities. These receptors are highly relevant to controlling a mammal's response to temperature changes, thus justifying more research [8]. Transient receptor potential (TRP) ion channels influence temperature detection and regulatory processes. Peripheral TRP channels interact with the autonomic nervous system whereas the detection of central temperatures is carried out by central TRP channels. Their gating is temperature dependent, this does not necessarily translate to thermoregulatory processes. Of the many isoforms of TRP channels, TRPM8 has been shown to play a role in cold-detection in the skin [8]. In a mouse knockout model, TRPM8 has been established to be a peripheral cold receptor detecting temperatures below 26°C [14]. While other isoforms of the TRP channel have been suggested to play a role in heat or cold detection and regulation of central thermoregulatory processes [8,15], Song *et al.* established that TRPM2 is present in a subset of POAH neurons and plays a part in detecting and controlling the internal body temperature, especially in conditions of fever and elevated temperatures [16]. Since elevated body temperature caused by hypermetabolism may occur after burn injury, this process could be relevant here Figure 2.

Metabolic derangements

Acute and long-term hypermetabolism is a hallmark of severe burn injury [17] and is accompanied by severe alterations in body composition, with muscle wasting due to an imbalance in protein synthesis and breakdown, loss of lean body mass and bone mineral content, increased resting energy expenditure, increased and inefficient cardiac output as well as inefficient heat production [17,18]. It has been shown that hypermetabolism persists for several years after the initial injury and therefore poses a systemic long-term challenge during prolonged recovery [6,17]. In paediatric patients, Hart *et al.* showed that resting energy expenditure remains elevated for up to 12 months after acute care. The group also showed that protein catabolism persists after burn injury for months, even after complete wound healing [19]. Similarly, growth retardation in children can be observed even years after the initial burn [20]. It is hypothesized that one function of post-burn catabolic hypermetabolism is to produce heat instead of conserving energy, and there is some pathophysiological molecular evidence to support this.

Recently, mitochondrial dysfunction in association with burn injury has been described in different organs including liver, adipose tissue, skeletal muscle and the heart [21–24]. In particular, the uncoupling of the mitochondrial respiratory chain and thus decreased adenosine-triphosphate (ATP) synthesis in favour of subsequent heat production via uncoupling proteins has been shown in animals and humans and is associated with pathological forms of compensatory heat production post-burn [18,21,22,25].

Mitochondria play a crucial role in the regulation of metabolism via ATP production, reduction of oxidative stress and calcium homeostasis. After burn injury, the interaction of increased oxidative stress, apoptosis and a disruption in respiratory activity and functionality can lead to cardiac dysfunction [23]. In a 2020 *in vivo* rat model, Wen *et al.* showed that genes related to mitochondrial metabolism in cardiomyocytes were severely altered 24 h after burn. The

authors described decreased electron transport chain activity and coupling state of mitochondria. This leads to uncoupling of the respiratory chain and causes a decrease in ATP and an increase in heat production [26]. Also, molecular pathways playing crucial roles in preserving mitochondrial function were shown to be altered by burn trauma [27,28]. Not only have cardiac mitochondria been shown to be altered, but also mitochondria in skeletal muscle, liver and adipose tissue [21,21,24], again pointing to the involvement of all organ systems in post-burn pathologies.

Experimental models of post-burn thermoregulation and metabolism

Several animal-based *in vivo* models have been developed to assess the complex mechanisms of thermodysregulation following burn injury. Most commonly, rats or mice are subjected to a full-thickness burn or scald injury and studied according to the researcher's interest [29,30]. Scald injuries are induced by placing the anaesthetized animal into a mold exposing the desired body surface area. Then, the animal is submerged into hot water. In most settings, animals receive fluid resuscitation with Lactate Ringer's solution and adequate pain management. Other methods to induce full thickness burn injuries use hot brass plates [31] or hot steam [32], typically to induce smaller TBSA burns. Table 1 summarizes all animal studies cited in this article.

To assess thermoregulatory processes, several methods may be used. Metabolic rate can be quantified by calorimetry in a sealed chamber under different environmental conditions, both in animals and human subjects. Calorimetry can be assessed directly via heat or indirectly via oxygen consumption, i.e. during mechanical ventilation [33,34]. In humans, exercise capacity may be determined by treadmill protocols and by analysis of expiratory gases O_2 and CO_2 [35,36]. The baseline of all measurements however, i.e. the accurate recording of the subject's body temperature, is crucial. In rodents, rectal temperature is commonly used although other methods such as infrared measurements may be applicable as well [37]. In burn patients, catheters placed in the bladder or central blood vessels are most common.

Using a methodologically elaborate setting, Herndon *et al.* first assessed in 1978 which animal model best mimics the human post-burn metabolic response [38]. The authors report that the ambient temperature and the extent of the injury significantly influence the metabolic response of adolescent and adult rats and adult guinea pigs when subjected to burn injury. Oxygen consumption was assessed as a proxy for hypermetabolism; it was shown that oxygen consumption of rats after a 50% TBSA scald-injury rose above the control group, measured at a thermoneutral temperature of 31°C. For smaller burns, hypermetabolism was less pronounced in warmer environments than in colder ones. In summary, with increasing TBSA affected, hypermetabolism became more severe and less dependent on environmental temperature. Similar observations may be made in humans

where raising the ambient temperature mitigates but does not prevent hypermetabolism in severely burned patients [38,39].

To assess thermoregulation after burn, Caldwell *et al.* conducted a series of experiments using rats with varying degrees of burn [40]. The group used a model in which the POAH was implanted with a perfusion apparatus as well as a cooling device to study heat production at different ambient temperatures. The authors report an upward shift of threshold temperature which may be caused by burn or lower ambient temperatures both in burned and control animals. Burned animals placed in colder environments are especially susceptible and the degree of change depends on the severity of the burn [40]. By cooling the POAH of burned and control rats, it was shown that heat production and plasma levels of epinephrine and norepinephrine rose in both groups. This shows the POAH's important involvement in temperature regulation and that central cooling greatly affects it [41]. Further studies have shown that the ambient temperature at which burned rats are housed greatly affects the degree of post-burn hypermetabolism and overall survival [37,42]. Caldwell *et al*. described that the thermosensitivity of the POAH is not altered by burn injury [40] but that a destruction of POAH severely impairs the injured animal's thermoregulatory ability, again proving the pivotal importance of the POAH [43]. This effect was found to be especially pronounced in colder environments (22°C) in which the rats became hypothermic. This reduced the tolerance for changed ambient temperatures and impaired the metabolic response [43].

In larger animal models, sheep and pigs are used. Pigs are mostly used to study aspects such as wound healing [44,45] and body temperature is only occasionally recorded; however, it has been shown to increase from baseline after burn injury induction [46]. Also, increased body temperature in swine as an indicator for systemic inflammatory response syndrome was described in a study researching the burn's effects on the whole organism [47] as well as during the inflammatory processes after burn [48]. Sheep are very commonly used to study inhalation injuries after burn trauma [49–51] but not frequently in researching thermoregulation.

Clinical aspects of post-burn thermoregulation

Hypothermia is defined as a body core temperature <35°C [52] and occurs when the patient loses more heat than the metabolic system is able to provide [53]. It occurs not only in burn patients but quite commonly during general anaesthesia [54,55] and in trauma patients [52]. Thus, in a variety of patients implementation of adequate temperature management strategies is crucial. Since patients having sustained severe burn injuries (>20% TBSA) exhibit significant loss of skin as a thermal barrier, which enables increased dry and wet heat loss [11,56], these patients are particularly prone to hypothermia. This is further aggravated by systemic hypermetabolism, the requirement for several operative procedures,

Table 1. Summary of animal models used in assessing thermoregulation after burn trauma

Study title	Species	TBSA	Induction method	Reference
Development and analysis of a small animal model simulating the human postburn hypermetabolic response	Growing rats, adult rats and growing guinea pigs	20–50%	Scald injury in 99°C water	[38]
Alteration in temperature regulation induced by burn injury in the rat	Male Sprague_ Dawley (SD)rats	31 ± 3%	Scald injury in 90°C water	[40]
The response in heat production, plasma catecholamines, and body temperature of burned rats to hypothalamic temperature displacement	Male SD rats	33 ± 4%	Scald injury in 90°C water	[41]
The effect of ablation of the preoptic anterior hypothalamus on energy metabolism and plasma catecholamines after burn injury in the rat	Male SD rats	23%	Scald injury in 90°C water	[43]
The genetic evidence of burn-induced cardiac mitochondrial metabolism dysfunction	Male SD rats	60%	Scald injury in 95–100°C water	[26]
Cardiac dysfunction after burn injury: role of the AMPK-SIRT1 PGC1α-NFE2L2-ARE pathway	Male SD rats	60%	Scald injury in 95–100°C water	[27]
Burn-induced cardiac mitochondrial dysfunction via interruption of the PDE5A-cGMP-PKG pathway	Male SDrats	60%	Scald injury in 95–100°C water	[28]
Design and testing of an experimental steam-induced burn model in rats	Male Wistar rats	1%	Hot steam	[32]
Core body temperature responses immediately after cutaneous thermal injury in rats	Female CD rats	20% and 40%	Scald injury in 100°C water	[42]
An optimized animal model for partial and total skin thickness burns studies	Male Wistar rats	4 cm^2	Contact burn via copper plate	[31]
Browning of white adipose tissue after a burn injury promotes hepatic steatosis and dysfunction	C57BL/6 and IL6−/− mice	30%	Scald injury in 98°C water	[22]
Burn induces browning of the subcutaneous white adipose tissue in mice and humans	Male C57BL/6 mice	30%	Scald injury in 98°C water	[21]
Platelet and coagulation function before and after burn and smoke inhalation injury in sheep	Nonpregnant farm-bred ewes	20%	Flame burn via burner	[50]
Effect of bronchodilators on bronchial gland cell proliferation after inhalation and burn injury in sheep	Female, range-bred Merino sheep	40%	Flame burn	[49]
Altered systemic organ blood flow after combined injury with burn and smoke inhalation	Range-bred female sheep	40%	Flame burn via burner	[51]
The effect of ketanserin, a specific serotonin antagonist, on burn shock hemodynamic parameters in a porcine burn model	Immature Yorkshire pigs	45%	Scald injury in 90°C water	[46]
Impact of isolated burns on major organs: a large animal model characterized	Female Yorkshire pigs	40%	Contact injury	[47]
Effect of TNF-α concentration on selected clinical parameters of swine after burns	Polish Landrance mixed-sex pigs	30 ± 2%	Contact injury via heating plate	[48]
Growth factors in porcine full and partial thickness burn repair. Differing targets and effects of keratinocyte growth factor, platelet-derived growth factor-BB, epidermal growth factor, and neu differentiation factor	Young, adult, female Yucatan micropigs	20 burns of 2.5 cm diameter	Contact injury	[44]
Study on the debridement efficacy of formulated enzymatic wound debriding agents by *in vitro* assessment using artificial wound eschar and by an *in vivo* pig model	Female Yorkshire-cross pigs	20 burns of 2 cm diameter	Contact injury via heated brass rod	[45]

CD cesarean-derived, *TNF-α* tumor necrosis factor-α, *TBSA* total body surface area

mechanical ventilation, massive fluid resuscitation and blood products [6,9,57]. Keeping these possible complications in mind, every hospital treating severely burned patients should have a clear understanding of necessary treatment strategies to prevent hypothermia. In-hospital hypothermia occurs not only in burn patients but also during general anaesthesia, which adds up to another level of risk when severely burned patients require multiple surgical procedures.

Among others, reasons for surgery-associated hypothermia are the autonomic changes in thermoregulatory processes caused by general anaesthesia [58]. Prominently, perioperative hypothermia is associated with a general decline in coagulation function [11], manifesting in increased blood loss and a higher risk of needing blood transfusions, even under conditions of mild hypothermia. This may in part be due to platelet dysfunction, as shown by Valeri *et al*. in *in vitro* and *in vivo* studies [59]. Coagulopathy, hypothermia and acidosis are called the 'lethal triad' and occur in trauma as well as burn patients. In both patient groups, it is associated with a higher mortality and poor prognosis [60]. Post-operative ventricular tachycardia and perioperative morbid cardiac events were shown by Frank *et al*. to occur less frequently if normothermia is achieved perioperatively, especially in patients already bearing risk factors for cardiac diseases [61]. Furthermore, hypothermia has been shown to be associated with delayed wound-healing and a predisposition for wound infections [62] in general surgery. With Kurz *et al*. having shown similar results for surgical wounds, the process might be of even greater impact in the treatment of burn wounds which tend to be more extensive and deeper [62]. Prehospital cooling of minor burn wounds with cold water is a common first-aid measure and does not seem to cause severe hypothermia in patients with mild burns who are not anaesthetized [63]. However, in severely burned patients, the risks of prehospital cooling increase significantly with burn severity, expressed by TBSA and full-thickness depth, the presence of inhalation injury, as well as the need for pre-hospital intubation and anaesthesia [52,63,64]. Among practices currently executed in the prevention and treatment of burn-associated hypothermia is raising the ambient temperature in preclinical rescue vehicles, as well as in the operating room (OR) and the intensive care unit (ICU), staged excision and grafting, limiting operating time if possible [65,66] and administering warm fluids [67,68]. Ideally, all vehicles and rooms in which the burn patient is treated are heated and closely connected to prevent cooling during transportation [69]. In non-burn associated surgeries, warming devices are commonly used to keep the patients' temperature from declining. In burn surgery, maintaining a stable body temperature is more difficult because large portions of the patient's body are within the sterile field to either access the burn wound or donor sites, making warming the patient via forced-air and warm-water circulating devices a challenge as the warming systems should not be placed directly on a burn wound [70,71]. If the aforementioned options are inefficient due to the severity of injury, invasive warming devices may be considered, although this is rarely necessary. Oesophageal heat-exchange devices can be placed directly in the oesophagus and may contribute to temperature maintenance [72,73]. Corallo *et al*. described a warming device placed in the inferior vena cava which provides active core warming to the patient [74] and has been shown to produce desirable results [75]. Invasive systems should be reserved however for severely burned patients due to the associated risks. While the strategies mentioned try to maintain a patient's heat and prevent cooling and hypothermia, they do not alter the burn-induced hypermetabolism. With increased understanding of the pathophysiological processes after burn injuries, the search for efficient and safe pharmaceutical means to combat hypermetabolism and alter thermoregulation is progressing. The beta-blocker propranolol has been used to modulate the adrenergic stress response and has been shown to blunt hypermetabolism [18] and decrease heart rate and resting energy expenditure in burned children [76].

Regarding the catabolic state of high energy consumption during the acute phase after trauma, it is of great importance to provide patients with high-caloric and protein-rich enteral nutrition from the onset of their treatment. Additionally, catabolic hypermetabolism may further be mitigated with the use of anabolic and anticatabolic drugs such as testosterone or oxandrolone [66] while recombinant human growth hormone has also been investigated in this capacity [18], all aiming to reduce protein catabolism and restore hormonal balance. Recombinant human growth hormone has been shown to stimulate wound healing, both of the actual burn wound and of the donor site for skin grafts, although study populations are often small and substantial bias exists [77].

Discussion

Adequate temperature management has long been established to be a fundamental principle in emergency medicine. Not only in burn injury but also in other sorts of trauma, maintenance of normothermia is crucial and advised [78,79]. Hypothermia is a part of the aforementioned lethal triad not only in burn patients, but generally. Especially during general anaesthesia, hypothermia can lead to adverse cardiac events or to delayed wound healing [61,62]. Thus, adequate temperature management is not only an issue in burn patients. As described earlier, many strategies to prevent hypothermia are available today, most commonly using hot devices and warmed fluids. In severely burned patients, more invasive approaches like placing a warming device in the inferior vena cava might become necessary [74] but should be reserved for specialized burn centres however. In summary, burn injury poses a unique pathophysiology, making adequate temperature management necessary but also a great challenge. While the regulatory mechanisms of body temperature controlled by the central nervous system have long been known, new aspects such as research about the TRP ion channels has picked up speed and shows promise in understanding molecular mechanisms and patterns of thermoregulation. TRPM2

and 8 in particular have been shown to be involved in these processes [8,14,16], but certainly considerably more research needs to be carried out to reach a fuller understanding of their function and effects on temperature regulation, especially central elements such as the POAH. Also, the exact reason why burn injury impairs thermoregulatory functions is still not clear. Alteration to the system could either be caused by a change in central thermosensitivity or by global metabolic changes. The research done by Caldwell *et al.* has provided important insights into the POAH's sensitivity after burn injury and revealed that it was not changed by the burn injury [40]. Thus, other mechanisms seem to be responsible. Among these, changes in metabolic function such as alterations in mitochondrial function seem probable. The uncoupling of the mitochondrial respiratory chain leads to heat production instead of ATP production. This phenomenon has been described in burn patients and animal models alike [22,80] and is associated with mitochondrial damage and functional derangement as described earlier [26]. Since this mitochondrial dysfunction is closely associated with pro-inflammatory signalling and the adrenergic stress response, both well described after burn injury [6,17,80], it seems to play a crucial role in understanding hypermetabolism and thus altered thermoregulation. Additionally, it has been described in several organs, e.g. the heart, liver and fatty tissue [21–23], thus highlighting the effects burn injuries have on different organs and the connection between the organs. Post-burn hypermetabolism is mainly driven by catecholamines and elevated concentrations of glucocorticoids such as cortisol, which have been shown to be elevated in the long-term context of burn injuries [6,17]. This leads to increased energy expenditure, prolonged loss of lean body mass [19] and growth retardation in children [20]. Therefore, adequate management in the acute phase and long-term is crucial and could improve metabolic function and therewith also temperature regulation.

Because of these needs, new approaches have been established in the last years. A 6-month course of the anabolic drug oxandrolone was shown to increase net deposition of skeletal muscle protein in a paediatric patient group [81]. In the acute phase after burn injury, oxandrolone has also been shown to lead to improved protein synthesis in muscle tissue [82], shorten hospital time and help maintain lean body mass [83]. Another study described diminished resting energy expenditure after oxandrolone treatment as well as an increase in lean body mass and muscle strength. Thus, the authors conclude that oxandrolone treatment aids burned children in recovery [84]. All these effects seem beneficial and may be summarized as reducing the hypermetabolic effects after burn injuries.

Another medication possibly blunting the hypermetabolic response are beta blockers. Nonselective adrenergic beta blockers like propranolol act by blocking the effects of catecholamines, lowering heart rate and cardiac work load [85]. The administration of propranolol 1 year after burn showed a diminished predicted resting energy expenditure and heart rate in children [86]. Similar findings were reported after short-term use of propranolol as study participants with severe burns showed reduced a heart rate and energy expenditure and increased net muscle protein balance [76]. Uncertainties about whether propranolol treatment might have negative effects on temperature regulation in burned children were addressed by Rivas *et al.* who showed that therapeutic doses of propranolol did not alter skin blood flow, which is an important measure for heat dissipation and conservation to regulate body temperature [35,36]. Both drugs provide a relatively new approach to post-burn care. Unlike heat-preserving methods, such as increased ambient temperature or heating devices, they aim to alter the pathophysiological source of the heat loss, namely the hypermetabolism. Thus, they possess great promise and possibly provide a more efficient method than exclusively treating the symptoms of hypermetabolism. While desirable results have been seen in children, few studies researching the drugs' effects in adults exist [87], thus creating a void which should be filled with appropriate studies in the future. Despite the beneficial effects of drugs however, Porter *et al.* call for the systematic expansion of rehabilitative exercise training to build and strengthen muscle mass, as well as to allow for close evaluation of the long-term nutritional and metabolic state of burn patients [18,66]. Because of the severity and long-time effects of burn injuries, this seems a valuable suggestion.

Overall, the findings discussed here highlight not only the association between mitochondrial damage and organ dysfunction or hypermetabolism and thermodysregulation but in generally the organ crosstalk between the multiple systems involved in and affected by burn injury. It is crucial to comprehend the multi-layered effects burn injuries have on the whole organism that warrant broader research approaches. In particular, the influence burn injuries have on central and peripheral thermoregulation need to be uncovered. Perhaps by combining findings regarding the importance of the POAH with possible mitochondrial damage, disturbances in organ crosstalk as well as the diverse functions of TRP, a more in-depth understanding may be achieved. Much as the studies by Caldwell *et al.* examined the influence of burn injury on the POAH, researching the response of TRP ion channels after burn could provide important insights.

Conclusions

With burn injuries posing a massive systemic threat for all organ systems, understanding the crosstalk between the different systems plays a crucial role in grasping the underlying pathophysiological alterations. The results of the available *in vivo* animal models provide important insights into the mechanisms of thermoregulation and their alterations through burn injury sequelae (hypermetabolism, increased set-point temperature, decreased thermoregulatory capacities). However, further efforts into investigating the changes to central thermoregulation, efferent and afferent signalling and their translation into peripheral thermoregulation need to be made.

The key concepts presented in this systematic review highlight the interwoven pathophysiology at play and might assist clinicians in optimizing treatment strategies for their patients.

Abbreviations

ATP: Adenosine triphosphate; POAH: Preoptic anterior hypothalamus; TBSA: Total body surface area; TRP: Transient receptor potential.

Authors' contributions

VM and GH conducted the database search and wrote the manuscript. All authors analysed and interpreted the data, reviewed and contributed significantly to the manuscript and read and approved the final manuscript.

Conflict of interest

None declared.

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