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Post-burn hypermetabolism: past, present and future

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Abstract

Hypermetabolism is the ubiquitous response to a severe burn injury, which was first described in the 19th century. Despite identification of important components of this complex response, hypermetabolism is still not well understood in its entirety. This article describes this incredibly fascinating response and the understanding we have gained over the last 100 years. Additionally, this article describes novel insights and delineates treatment options to modulate post-burn hypermetabolism with the goal to improve outcomes of burn patients.

Keywords

burn injury; hypermetabolism; inflammation; stress

1. Introduction

There are over 300,000 deaths worldwide due to a burn injury [1]. In the United States over 500,000 burn injuries occur every year resulting in 40,000 to 60,000 admissions to a hospital or burn center for appropriate treatment. Over the last 40 years burn outcomes improved significantly, due to establishing specialized burn centers and profound advances in therapy strategies, such as improved resuscitation, implementation of burn specific critical care protocols, fast and more adequate wound coverage, more appropriate infection control, improved treatment of inhalation injury and better support of the hypermetabolic response [2,3]. However, severe burns remain an injury that affects nearly every organ system and that leads to a substantial morbidity and mortality [2-6]. Deaths in burn patients generally occur either immediately after the injury or weeks later as a result of infection/sepsis, multi-system organ failure or hypermetabolic catabolic responses [3,7]. It is interesting to note that over the last decade cause of death changed profoundly [7]. Cause of death in severely burned patients used to be due to anoxic brain injury, followed by sepsis, and multi organ failure. Nowadays the major cause of death in burned patients is sepsis followed by multi organ failure and anoxic brain injury [7]. As increased sepsis and infection, as well as MOF are usually strongly linked with hypermetabolism these data indicate that hypermetabolism is

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not only directly but also indirectly related with poor outcomes after burn. This article aims to review the past of hypermetabolism after burn, the physiology of hypermetabolism, indicate current treatment options, and lastly to speculate on the future of hypermetabolism.

2. Hypermetabolism after burn

The observation that trauma in general can induce profound alterations in metabolism was already documented in the 19th century when Claude Bernard described a state of “diabète traumatique” during hemorrhagic shock [8]. In 1943 Taylor et al described the abnormal nitrogen metabolism in burns [9]. Keyser conducted some very important metabolic studies of burn patients in in the 1940s describing the pathophysiology of hypermetabolism [10]. Truman Blocker conducted some very important and sophisticated studies in the 1950s identifying essential steps in protein metabolism after burn using radioactive labelled albumin [11]. Numerous landmark papers [12-19] followed in the second half of the 20th century looking into more in depth cause and associations and truly manifesting post-burn hypermetabolism as a major contributor to post-burn morbidity and mortality.

2.1. Pathophysiology of Hypermetabolism

Hypermetabolism leads to vast catabolism which is associated with protein breakdown not only in muscle but also in almost every organ leading to multi organ dysfunction [20-22]. Therefore we suggest that hypermetabolism and organ function and consecutively survival are closely linked with each other. The hypermetabolic response post-burn is not only very profound but also extremely complex and is most likely activated and sustained by stress induced hormonal releases and inflammation [5,6,23,24]. The cause of this response is not entirely defined but it appears that an increased and prolonged expression of catecholamines, glucocorticoids, glucagon and dopamine are involved in initiating and maintaining this complex response which if untreated inevitably leads to a profound catabolic state [20,23,25-33]. In addition, cytokines, endotoxin, neutrophil-adherence complexes, reactive oxygen species, nitric oxide and coagulation as well as complement cascades have also been implicated in mediating this response to burn injury [34]. Others and we believe that once these cascades are initiated after burn, their mediators and by-products appear to further stimulate the persistent and increased metabolic rate associated with altered glucose, lipid, and amino acid metabolism [35].

The metabolic changes post-burn occur in two distinct pattern of metabolic regulation following injury [36]: the “ebb phase” usually occurs within 48 hours post-burn [36,37] and is characterized by decreased cardiac output, lower oxygen consumption, and lower metabolic rate. The lower metabolic response (hypo-metabolism) then gradually increases within the first five days post-injury to a plateau phase: flow phase; this phase is characterized by a hyperdynamic circulation, increases in body temperature, oxygen and glucose consumption, CO_2 production, glycogenesis, proteolysis, lipolysis, and futile substrate cycling. Insulin release during this time period was found to be twice that of controls in response to glucose load [38,39] and plasma glucose levels are markedly elevated, indicating the development of an insulin-resistance [6,40,41]. In addition lipolysis is substantially increased leading to increased free fatty acids and triglycerides [6,42]. Current understanding has been that these metabolic alterations resolve soon after complete wound closure. However, recent studies found that

the hypermetabolic response to burn injury lasts significantly longer. We [23] found that various biomarkers indicative of an increased hypermetabolic response are significantly and persistently elevated for up to 3 years. We showed that total urine cortisol levels, serum cytokines, serum catecholamines, and basal energy requirements were significantly increased for up to 3years [23] and accompanied by impaired glucose metabolism and insulin sensitivity [43]. These results indicate the importance of long-term follow-up and treatment of severely burned patients.

As the hypermetabolic response involves a vast number of pathways, including hyperinsulenimic hyperglycemic response indicative of profound insulin resistance,[44-47] as well as lipid metabolism with increased lipolysis [48-51] and amino acid-protein-metabolism [5,6,23,24] we will discuss each of these in more detail below.

2.2. Glucose metabolism

During the early post-burn phase, hyperglycemia occurs as a result of an increased rate of glucose appearance, along with an impaired tissue extraction of glucose, leading to an overall increase of glucose and lactate.[52,53] Of major importance is recent evidence strongly suggesting that hyperglycemia is detrimental and associated with adverse clinical outcomes in severely burned patients. Hyperglycemia is associated with increased infections and sepsis, increased incidence of pneumonia, significantly increased catabolism and hypermetabolism, and, most importantly, with increased post-burn mortality.[44-47,54,55] The evidence that hyperglycemia is detrimental in burn patients was further supported by a prospective randomized trial that showed that glucose control is beneficial in terms of post-burn morbidity and organ function.[47] Retrospective cohort studies further confirmed a survival benefit of glucose control in severely burned patients.[46,55] These data strongly indicate that IR and hyperglycemia represent a significant clinical problem in burn patients and are clearly associated with poor outcomes.

Although the dire consequences of burn-induced hyperglycemia have been delineated, the molecular mechanisms underlying IR and hyperglycemia are essentially unknown. Therefore recent studies focused on the identification of molecular mechanisms that lead or are associated with IR and hyperglycemia. As the ER stress response was identified as one of the central intracellular stress signaling pathways linking IR, hyperglycemia, and inflammation in diabetes [56] and based on animal experiments, we asked the question whether burn induces ER stress and the unfolded protein response (UPR) in severely burned patients [6]. As hypothesized, we found that a severe thermal injury induces ER stress in the metabolically active tissues skin, fat, and muscle.[57] Additionally, we have recently shown that burn is not only associated with induction of ER stress but furthermore with activation of the adipose localized NLRP3 inflammasome which augments inflammation and increases IR and hyperglycemia [58]. These interlinked responses may be mechanistically linked with the induction of post-burn hypermetabolism. But of greater importance is that scientists now realize that novel treatment approaches have to be derived from novel approaches and insight based on cellular or genomic responses.

2.3. Fat metabolism

The other metabolic pathway that is significantly altered during the post-burn hypermetabolic response is lipid metabolism, which may be related to changes in insulin resistance. Lipolysis consists of the breakdown (hydrolysis) of triacylglycerol into free fatty acids (FFA) and glycerol. Notably, lipolysis and free fatty acids not only contribute to post-burn morbidity and mortality by fatty infiltration of various organs, but it was also shown that FFAs can mediate insulin resistance.[59] Specifically, FFAs impair insulin-stimulated glucose uptake[60,61] and induce insulin resistance through inhibition of glucose transport activity.[62] In the context of type 2 diabetes, it has been shown that increased FFA levels are predictive for incidence and severity of the disease.[63] One of the major alterations post-burn is significantly increased lipolysis, and several studies have suggested that increased lipolysis can be attributed to increased catecholamine levels.[18,64] Interestingly, despite increased lipolysis, plasma FFA concentrations can be increased or decreased which can be due to hypo-albuminemia or increased intracellular FFA turnover, which is part of the futile cycle involving the breakdown of adipose and muscle TGs into FFA. Regardless, increased triglycerides and FFA lead to fatty infiltration of vital organs, especially the liver. Accordingly, fatty liver is very common post-burn and is associated with increased clinical morbidities, as well as metabolic alterations. Post-burn pathology examinations [65,66] and spectroscopy studies have shown that burned children have a 3 to 5-fold increase in hepatic triglycerides,[67,68] associated with increased incidence of infection, sepsis, and poor outcome [51]. Kraft et al. conducted a recent clinical analysis about the association between post burn FFA and TG with clinical outcomes in severely burned children. The authors found that in severely burned children elevated TGs are associated with worsened organ function and clinical outcomes as well as glucose metabolism [42]. This data is in agreement with various other recent studies that showed a strong relationship between fat and glucose metabolism.[69] Though this relationship is clear, the mechanism by which lipids induce insulin resistance is not entirely defined. The adipose tissue was ignored as a contributor to the hypermetabolic response for a long time, but it is increasingly evident that the adipose tissue plays a very central role in mediating not only metabolic but also inflammatory responses.

2.4. Protein metabolism

Protein/amino acids from skeletal muscle is the major source of fuel in the burned patient, which leads to marked wasting of muscle protein and consequently of lean body mass (LBM) within days after injury [5,70]. The underlying pathophysiology was shown to be a substantial increase in muscle protein breakdown along with no or only a minor compensatory increase in muscle protein synthesis leading to muscle loss. Depending on the degree of muscle protein loss the clinical consequences can reach from infections to death and can be quite severe. A 10-15% loss in lean body mass has been shown to be associated with significant increases in infection rate and marked delays in wound healing. A further increase in loss of LBM leads to profound increased morbidity and with a LBM loss of approximately 40% even mortality [71]. The resultant muscle weakness was further shown to prolong mechanical ventilator requirements, inhibit sufficient cough reflexes and delay mobilization in protein-malnourished patients, thus markedly contributing to the incidence of mortality in these patients [72]. Persistent protein catabolism may also account for delay in

growth frequently observed in the pediatric patient population for up to two years post-burn [23]. Additionally, since skeletal muscle has been shown to be responsible for 70-80% of whole body insulin-stimulated glucose uptake, decreases in muscle mass may contribute to this persistent insulin resistance post-burn [73].

Of note is, that we have recently shown that body composition pre-existing to the burn can determine outcomes. Using the platform and database of the Glue Grant we found that mild obesity determined by BMI calculation has improved survival and outcomes when compared to normal BMI when risk adjusted [74]. The worse outcomes have patients that are malnourished and cachectic or the morbidly obese ones indicating that the pre-injury nutritional status affects outcomes after a burn injury.

3. Treatment of the hypermetabolic response

It is very interesting to note that at the beginning of the 20th century once the metabolic response to burn was recognized, clinicians and scientists initiated possible perturbation to reduce post-burn hypermetabolism. Shaffer and Coleman suggested the use of high caloric feeding for burn patients at the beginning of the 20th century, which was adapted Wilmore et al [75], suggesting up to 8000 kcal/day, and Curreri et al, suggesting 25 kcal/kg body weight plus an additional 40kcal/%TBSA burn [76]. Nowadays our feeding regimens are usually based on resting energy expenditure and an additional stress factor, but it is still being discussed [77-79]. Not only is the caloric amount currently under discussion, but furthermore the composition of the nutrition as well as other adjuncts. Already in 1946 Abbott et al described the use of a different amount and composition as well use of testosterone on the negative nitrogen balance [80].

3.1. Nutrition

Nutrition has and remains a controversially discussed topic but is nonetheless essential to alleviate hypermetabolism. But the primary goal of nutritional support is to provide an adequate energy supply and the nutrients necessary to maintain organ function and survival. Early adequate enteral nutrition alleviates catabolism and improves outcomes [81], however, overfeeding, in form of excess calories and/or protein is associated with hyperglycemia, carbon dioxide retention, fatty infiltration of organs, and azotemia [70]. Therefore, nutrition is an essential component to alleviate hypermetabolism, but too much feeding is detrimental and it therefore imperative to calculate the caloric requirements as accurately as possible. Currently, resting energy requirements of burned patients are commonly estimated using equations that incorporate body mass, age, and gender [77-79]. However these equations although based on patient-specific factors may significantly overestimate caloric requirements increasing the risk of overfeeding [82,83]. Recently the adapted Toronto equation seems to be a better formula to calculate REE, as the calculated results very closely matched the MREEs. In general adequate nutrition is an essential component in burn care and should be initiated within 12 hours after injury [84].

At the moment no ideal nutrition for burn patients exists and there is no gold standard. Others and we recommend the use of a high glucose, high protein/amino acid, low fat nutrition with some unsaturated fatty acids [77-79]. We believe that the major energy source

for burn patients should be carbohydrates and amino acids thereby sparing protein from oxidation for energy, allowing the protein to be effectively used by the skin and organs. Single amino acid supplementation was and is controversially discussed, especially alanine and glutamine. Glutamine is quickly depleted post-burn from serum and muscle [85,86], however this depletion mainly occurs intracellular and it is very difficult to deliver Glutamine effectively to the cells. Small studies in burn patients indicated that Glutamine supplementation decreased incidence of infection, length of stay and mortality [85,86]. Therefore there is a signal that Glutamine supplemental maybe associated with beneficial effects. A current multicenter trial (REDOX) is addressing the answer and the results are expected over the next 4-5 years. The literature on Alanine is even sparser and at this time there is no evidence to administer or not administer Alanine. Lastly, components that recently gained attention are vitamins, micronutrients and trace elements [87]. Plasma levels of vitamins and trace elements are significantly depressed for prolonged periods after the acute burn injury due to increased urinary excretion and significant cutaneous losses. Replacement of these micronutrients lessens morbidity in severely burned patients [88-94]. Therefore, a complete daily multi- vitamin / mineral supplementation should be given.

3.2. Other non-pharmacological strategies

Early excision and closure of the burn wound has been probably the single greatest advancement in the treating patients with severe thermal injuries during the last two decades leading to substantially reduced resting energy requirements and subsequent improvement of mortality rates [5,95,96]. It is in our opinion imperative to excise the burn wounds early, within 72 hours after burn, and cover the excised areas with temporary cover materials or autologous skin. This will decrease the burn induced inflammatory and stress responses leading to decreased hypermetabolism.

The altered physiologic state resulting from the hypermetabolic response attempts to at least partly generate sufficient energy to offset heat losses associated with this inevitable water loss. The body attempts to raise skin and core temperatures to 2°C greater than normal. Raising the ambient temperature from 25 to 33°C can diminish the magnitude of this obligatory response from 2.0 to 1.4 resting energy expenditure in patients exceeding 40% TBSA. This simple environmental modulation, meaning raise room temperature is an important primary treatment goal that frequently is not realized [97].

A balanced physical therapy and exercise program is a crucial yet easy intervention to restore metabolic variables and prevent acute and long-term adverse sequelae. Progressive resistance exercises in convalescent burn patients can maintain and improve body mass, augment incorporation of amino acids into muscle proteins, and increase muscle strength and endurance [82,98]. It has been demonstrated that resistance exercising can be safely accomplished in burn patients without exercise related hyperpyrexia [82,98].

3.3. Pharmacologic modalities

3.3.1. Recombinant human Growth hormone—Daily intramuscular administration of recombinant human growth hormone (rhGH) during acute burn hospitalization has been shown to have a plethora of effects on post-burn hypermetabolism and inflammation [99,100].

RhGH has profound anabolic effects on muscle and skin[95,101,102] by either direct effects via the GH receptor or via indirect effects via increased insulin like growth factor-I (IGF-I) [103]. RhGH therefore seemed to be an ideal treatment option for post-burn hypermetabolism, however, in a prospective, multicenter, double-blind, randomized, placebo-controlled trial involving 247 patients and 285 critically ill non-burned patients Takala et al. found that high doses of rhGH were associated with a substantial increased morbidity and mortality [104] and the use of rhGH was therefore restricted. This exact mechanisms of this increased mortality is not entirely defined but among other effects rhGH causes hyperglycemia and insulin resistance [105,106] and was previously mentioned hyperglycemia by itself causes increased morbidity and mortality in burn patients. In follow-up studies in burn patients neither short nor long-term administration of rhGH was associated with an increase in mortality in severely burned children [27,107]. But at this time rhGH is not recommended for burn patients.

3.3.2. Insulin-like growth factor—The effects of IGF-I on burn responses was initiated in part because GH increases IGF-I levels and it is not evident whether the beneficial effects of rhGH are due to GH or IGF-I. IGF-I administration in animals had anti-inflammatory, alleviation of stress responses, and anabolic effects. Because IGF-I when given alone has profound side-effects a new complex was developed in which IGF-I was bound in a 1:1 molar ratio to its binding protein (IGFBP-3). In severely burned patients IGF-I/BP-3 improved protein metabolism and attenuated catabolism with significantly less effects on hypo- (insulin) or hyperglycemia (rhGH) [108]. IGF-I/BP-3 attenuates muscle catabolism by decreasing muscle protein breakdown, improved gut mucosal integrity, improved immune function, attenuate acute phase responses, and decreased inflammatory responses [108-111]. However we observed that the complex of IGF-I/BP-3 increased neuropathies in severely burned patients and until this is further investigated IGF-I/BP-3 is on hold for clinical use at this moment. It is interesting to note, that other investigators demonstrated that the use of IGF-I alone is not effective in critically ill patients without burns indicating that IGF-I only exerts its effects when either IGF-I levels are low or the presence of a hypermetabolic induced high IGF-I turnover leading to an IGF-I deficiency. At this time, IGF-I is considered an experimental drug at this time. But modification of the IGF-I protein complex may result in a novel drug that is both safe and efficacious.

3.3.3. Oxandrolone—An anabolic agent that was introduced three decades ago but still is poorly explored is oxandrolone. Oxandrolone is a testosterone analog which possesses only 5% of its virilizing androgenic effects. In burn patients treatment with oxandralone improves muscle protein catabolism via an increase in protein synthesis [112], reduce weight loss and increases donor site wound healing [113]. In a large prospective, double-blinded, randomized single-center study, oxandrolone shortened length of acute hospital stay, maintained LBM associated with improved body composition, and improved hepatic protein synthesis [114]. In a multi-center prospective randomized study Wolf and colleagues demonstrated that administration of 10 mg of oxandralone BiD decreased hospital stay and affected morbidity and mortality [115]. The effects were independent of age [116,117]. Oxandrolone seems not only to be a short term acute intervention, but it appears that long-term treatment with oxandrolone decreased chronically elevated hypermetabolism, and significantly increases

lean body mass at 6, 9, and 12 months, as well as bone mineral content at 12 months after burn compared to burned control patients [118,119].

A study in surgical patients however raised concerns about the use of oxandrolone in critically [120]. The authors found Ventilator-dependent surgical patients receiving oxandrolone had a more prolonged course of mechanical ventilation and may enhance collagen deposition and fibrosis in the later stages of acute respiratory distress syndrome and thus prolong recovery. Another critical issue is that oxandrolone may cause acute hepatic damage increasing liver enzymes [114]. Oxandrolone is a great option to alleviate catabolism for burn patients but its side effects need to be considered when it is being administered.

3.3.4. Propranolol—Beta-adrenergic blockade with propranolol represents probably the most efficacious anti-catabolic therapy in the treatment of burns. Augmented and increased catecholamines are the primary mediators to induce hypermetabolism [14-16]. It therefore became evident that blocking catecholamine receptor maybe beneficial. As the alpha-receptor blockade is not very well studied, the focus was so far on beta-adrenergic receptor blockade. It was repeatedly shown that acute administration of propranolol, a non-selective β1/β2 receptor antagonist, exerts anti-inflammatory and anti-stress effects [121]. Propranolol reduces skeletal muscle wasting and increases lean body mass post-burn [21,122] and improves glucose metabolism by reducing insulin resistance [123]. These effects or most likely associated with improved organelle function. Propranolol restores impaired mitochondrial dysfunction and alleviates burn induced ER stress [123]. Propranolol therefore seems to have stress reducing properties that lead to an attenuated hypermetabolic response. Propranolol not only has beneficial effects acutely, others and we also found that long-term administration of propranolol appears to have beneficial effects. Long-term propranolol treatment significantly reduced persistently increased heart rates as well as resting energy expenditure, decreased accumulation of central mass and central fat, prevented bone loss, and improved lean body mass [124]. It is important to note that there were very few adverse effects induced by propranolol. In appears, that propranolol acutely and long-term ameliorates the hyperdynamic, hypermetabolic, hypercatabolic, and osteopenic responses in pediatric patients [21,124,125] and therefore appears to be an adjunct with great potential. In light of the power of propranolol, a multi-center trial was initiated recently to study the effects of propranolol administration on short and long-term outcomes after burn injury.

3.3.5. Insulin—Insulin is a fascinating hormone because of its multi-factorial effects. Besides its ability to alter glucose metabolism, insulin has effects on fat and amino acid metabolism, is anabolic and enhances cell regeneration [47,126-129]. Its main effect is however to regulate glucose metabolism and it Ii well documented that burn induces a hyperinsulenimic hyperglycemic state that is similar to the pathophysiology of type 2 diabetes, differing only in its acute onset and severity [130]. This acute onset of stress-induced hyperglycemia is associated with adverse clinical outcomes after severe burn [44,45]. Burned patients with poor glucose control have a significantly higher incidence of bacteremia/ fungemia and mortality compared to burn patients who have adequate glucose control, as well as that hyperglycemia exaggerates protein degradation, enhancing the catabolic response [44,45].

Insulin therapy has been shown in various studies to be beneficial for burn patients [30,55,129,131-136]. In 2005, Pham et al [55] showed in a retrospective study that intensive insulin therapy lowers infection rates and improves survival. The study following was a cohort study from Hemmila et al. The authors found that intensive insulin therapy for burn-injured patients reduced the incidence of pneumonia, and decreased ventilator-associated pneumonia, and urinary tract infections [46]. We conducted and published the first prospective RCT in 2010; we enrolled almost 240 pediatric burned patients [47]. The primary outcome was mortality, secondary outcomes included infections, organ function, and endocrinology data. Due to an uneven randomization, we could not find a difference in mortality between groups ($p<0.14$), but we found that that tight glycemic control significantly decreased infection and sepsis, improved organ function, and alleviated burn-induced IR compared to control patients. Despite the non-significance for our primary outcome, this RCT indicated that insulin treatment has benefits in terms of post-burn morbidity for burn patients [47].

Intensive insulin therapy to maintain tight euglycemic control, however, represents a difficult clinical effort and has been associated with hypoglycemic episodes. Recent large clinical studies focused on insulin-induced hypoglycemia and its consequences: the VISEP trial found a 4-fold higher incidence of hypoglycemia; the GLUCONTROL trial found a 3-4-fold higher incidence; and the NICE SUGAR trial, a similar incidence. Marae et al reported recently in NEJM that tight glucose control in pediatric intensive care patients had no significant effect on clinical outcomes but led to increased incidence of hypoglycemia [137]. A recent retrospective study reported the relationship between mild (< 81 mg/dL) to severe (< 40 mg/dL) hypoglycemic episodes and death [138] and found that patients who had hypoglycemic episodes had a mortality of 36.6% compared with 19.7% in those who did not experience hypoglycemia. Once the authors adjusted for insulin therapy, hypoglycemia was independently associated with increased risk of death, cardiovascular death, and death due to infectious disease[138]. The NICE SUGAR trial group used their patients from the prior trial and determined whether hypoglycemia leads to an increased morbidity and mortality in ICU patients [139]. The authors were not able to prove a causal relationship between hypoglycemia and death but their data are strongly indicative that hypoglycemia in critically ill patients is associated with an increased risk of mortality.

Maintaining a continuous hyperinsulenimic, euglycemic clamp in burn patients is particularly difficult because these patients are being continuously fed large caloric loads through enteral feeding tubes in an attempt to maintain euglycemia. As burn patients require weekly operations and daily dressing changes, the enteral nutrition occasionally has to be stopped, which leads to disruption of gastrointestinal motility and the risk of hypoglycemia. Recent data from our center indicated that burn patients having one or more hypoglycemic episodes have a 9-fold increased odds ratio for mortality after burn, attesting to the profound detrimental outcomes of hypoglycemia [140]. We conducted a study to determine the ideal glucose target in severely burned children. We found that 130 mg/dl is the best glucose target, because of glucose levels below 150-160 mg/dl but avoiding detrimental hypoglycemia [141]. Therefore, we recommend at the current time to implement glucose control to a target of 130 mg/dl using insulin.

3.3.6. Other options—Newer potential mediators for post-burn hypermetabolism include a battery of agents, which the majority has not been studied thoroughly as a RCT in burn patients. Metformin (Glucophage), a biguanide, has recently been suggested as an alternative means to correct hyperglycemia in severely injured patients by inhibiting gluconeogenesis and improving peripheral insulin sensitivity [142,143]. Despite Metformin's very clearly described role in the diabetic population, its effects in burn patients are essentially unknown. To-date there are no large RCT's in burn patients but two small studies reported that metformin decreased endogenous glucose production, accelerated glucose clearance in severely burned and lead to increased fractional synthetic rate of muscle protein and improvement in net muscle protein balance [142,144]. The effects of metformin on clinical outcome are unknown but metformin seems to have an advantage over other anti-diabetic agents, as metformin does not cause hypoglycemia, thus possibly eliminating this concern associated with the use of exogenous insulin [142,145-147]. Despite the advantages and potential therapeutic uses, treatment with metformin, or other biguanides, has been associated with lactic acidosis [148]. Metformin is an interesting agent that may or may not have a role in regulating post-burn metabolism.

Other ongoing trials in order to decrease post-burn hyperglycemia include the use of Glucagon-Like-Peptide (GLP)-1 and PPAR-γ agonists (e.g., pioglitazone, thioglitazones) or the combination of various anti-diabetic drugs. PPAR-γ agonists, such as fenofibrate, have been shown to improve insulin sensitivity in patients with diabetes. Cree and colleagues found in a recent double-blind, prospective, placebo-controlled randomized trial that fenofibrate treatment significantly decreased plasma glucose significantly decreased plasma glucose concentrations by improving insulin sensitivity and mitochondrial glucose oxidation [67]. Fenofibrate also led to significantly increased tyrosine phosphorylation of the insulin receptor (IR) and IRS-1 in muscle tissue after hyperinsulinemic-euglycemic clamp when compared to placebo treated patients, indicating improved insulin receptor signaling [67]. GLP-1 has been shown to decrease glucose in severely burned patients but it was also shown that GLP-1 may not be sufficient to decrease glucose by itself and insulin needs to be given as an adjunct.

4. Future

Hypermetabolism is part of the body's ubiquitous response to burn. Over the last 70 years the burn community went from recognizing hypermetabolism, to alleviate hypermetabolism, to now asking the question what causes hypermetabolism. It seems very evident that hypermetabolism is present and plays a significant role for burn patient outcomes. Hypermetabolism is not outdated or unimportant at all, and seems more central for survival than ever. In order to successfully treat patients during the acute and long-term setting we need to understand the molecular and genetic changes that occur during this complex response. Recent studies attempted to determine mechanisms in animals and humans and found that burn causes profound alterations in cell organelles as well as cellular metabolic and inflammatory responses, which represent beginnings of our understanding about the hypermetabolic response. Modern technological examinations and advances will further enable new discoveries that may lead to mechanistic insights that will change the way we treat post-burn hypermetabolism.

5. Summary and Conclusion

The profound metabolic alterations post-burn associated with persistent changes in lipid and glucose metabolism, as well as impaired insulin sensitivity significantly contribute to adverse outcomes of burn patients. Even though advances in therapy strategies with the goal to alleviate the hypermetabolic response to burn have significantly improved the clinical outcome of these patients over the past years, therapeutic approaches to overcome and normalize this persistent hypermetabolism and associated hyperglycemia have remained challenging. Early excision and closure of the burn wound has been probably the single greatest advancement in the treating patients with severe thermal injuries during the last twenty years; leading to substantially reduced resting energy requirements and subsequent improvement of mortality rates in this particular patient population. At present, beta-adrenergic blockade with propranolol represents probably the most efficacious anti-catabolic therapy in the treatment of burns. Other pharmacological strategies that have been successfully utilized in order to attenuate the hypermetabolic response to burn injury include insulin; maintaining blood glucose at levels below 130 mg/dl using intensive insulin therapy has been shown to reduce morbidity in burn patients, however, are associated with detrimental hypoglycemic events, that have led to the investigation of alternative strategies, including the use of metformin and the PPAR-γ agonist fenofibrate. Nevertheless, further studies are warranted to determine the safety and the appropriate use of novel agents or even some of the above mentioned drugs in burn patients.

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