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The Role of Hyperglycemia in Burned Patients: Evidence-Based Studies

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Abstract

Severely burned patients typically experience a systemic response expressed as increased metabolism, inflammation, alteration of cardiac and immune function, and associated hyperglycemia. Hyperglycemia has been associated with an increased risk of morbidity and mortality in critically ill patients. Until recently and for many years, hyperglycemia has been expectantly managed and considered a normal and desired response of an organism to stress. However, findings reported from recent studies now suggest beneficial effects of intensive insulin treatment for critically-ill patients.

The literature on the management of hyperglycemia in severely burned patients is sparse, with most of the available studies involving only small numbers of burned patients. The purpose of this article is to describe the pathophysiology of hyperglycemia following severe burns and review the available literature on the outcome of intensive insulin treatment and other anti-hyperglycemic modalities in burned patients in an evidence-based-medicine approach.

Keywords

Burns; intensive insulin; glucose modulation; metformin; fenofibrate

INTRODUCTION

Burns are considered one of the most severe forms of trauma (1) with a severity, length, and magnitude unique to these patients (2). More than 500,000 burn injuries occur annually in the United States resulting in approximately 20,000 acute admissions to burn centers (3). Severely burned patients typically experience a systemic response including inflammation, increased metabolism, alteration of cardiac and immune function and hyperglycemia (4).

Stress-induced hyperglycemia (SIH) was observed more than 100 years ago, being first described by Claude Bernard as “diabète traumatique” during hemorrhagic shock (5, 6) and has been also named “diabetes of critical illness” (7) and “burn stress pseudo-diabetes” (8). Stress-induced hyperglycemia has been defined as plasma glucose levels >200mg/ml in non-diabetic patients occurring as a result of injury (9, 10), although it has also been characterized in the range >200mg/dL (9–11) to > 240mg/dL (4, 12) in different institutions.

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It has been observed following severe burns, trauma, myocardial infarction, stroke or surgery (5, 6, 13–15).

Hyperglycemia is an almost universal finding amongst patients suffering major burn injury. For many years, this condition was expectantly managed and considered as a normal and desired response (16–19). However, this non-treatment paradigm has recently shifted towards intervention and aggressive treatment of hyperglycemia in an attempt to improve survival and reduce complication rates (17).

The studies of Van den Berghe et al. reported improved survival and decreased morbidity in critically-ill patients by maintaining blood glucose levels at or below 110 mg per deciliter, through the use of intensive insulin regimens (20–22). Following these studies, tight glycemic control has become a perceived standard of care in critical illness (7), although concern has also risen regarding hypoglycemic events with this type of therapy (22, 23), especially when glucose is monitored with point-of-care glucometers (24).

Seventy-three percent of American Burn Association (ABA) verified burn centers have presently implemented intensive insulin practices using target upper limit glucose levels in the range <120 mg/dl in most of these units (24). However, when searching for the impact of tight glucose control on morbidity and mortality, most of the available literature about SIH describes mixed populations, where burned patients represent a small percentage of the studied patients when included, and leads to difficulty in evaluating the true benefit of reduced plasma glucose levels in this specific patient population.

The aim of this review is to investigate both the pathophysiology and the effects of hyperglycemia on burned patients, as well as to describe current therapeutic modalities and their outcomes in an evidence-based fashion, in an attempt to clarify whether there is sufficient evidence that anti-hyperglycemic treatment is beneficial, and the glucose range that should be aimed for in these patients.

PATHOPHYSIOLOGY OF STRESS-INDUCED HYPERGLYCEMIA

The excess presence of any substance can generally be explained by three conditions: excess of production; reduced clearance (intake or excretion); or the presence of both these conditions (Fig. 1). Hyperglycemia in severely burned patients results from a similar set of factors. Burned patients exhibit increased gluconeogenesis and glycogenolysis (increase of glucose production), as well as insulin resistance, leading to decreased glucose uptake and reduced clearance. The underlying mechanisms are not entirely defined, but multiple studies have indicated that SIH is associated with excessive release of catecholamines, cytokines, hormones, and acute phase proteins (10, 14).

Increased Glucose Production

The metabolic changes in burns occur in two different phases: the initial shock or “ebb” phase, present in the first five days, and the subsequent “flow” phase or hypermetabolic phase of injury (5, 16, 17, 25). During the ebb phase, activation of the sympathoadrenal and the hypothalamopituitary-adrenal axis occurs, leading to increased plasma levels of catecholamines, glucocorticoids and cytokines (26). This results in a significant increase of total glucose (27) but mass flow of glucose to peripheral tissue is only slightly altered (16). In the subsequent hypermetabolic flow phase of injury, mass flow of glucose to peripheral tissues increases, directed by sympathetic stimulation (16). Significant impairment of hepatic function is observed in these patients (28), but hepatic gluconeogenesis via Cori and alanine cycles is increased (10, 16, 25). A study in rodents has suggested that burn related hyperglycemia arises from glycogen breakdown and gluconeogenesis (29), and similar

findings were later described by Wolfe et al. in humans (30). Genes encoding for gluconeogenesis are known to be up-regulated as early as six hours after burn injury (31), whilst clinically, peak glucose levels are observed between the 2nd and 4th day post burn (4, 5, 32).

In addition to stress signals, various hormonal changes contribute to hyperglycemia in burned patients and are listed below:

- a. Epinephrine: elevated in burn patients (33, 34), increasing gluconeogenesis (skeletal muscle and hepatic); also causes insulin resistance by altering post-receptor signaling (10) and increasing lipolysis (10, 14).
- b. Norepinephrine: increases glucose production mainly by gluconeogenesis via glycerol production (lipolysis); and to a lesser extent than epinephrine, by increasing glycogenolysis (10, 14, 33).
- c. Glucagon: known to stimulate glucose production by increasing hepatic gluconeogenesis and glycogenolysis (5, 10, 14, 35–37). Jahoor et al. found that in severely burned patients, hyperglucagonemia stimulates increased glucose production, and that selective lowering of glucagon normalized glucose kinetics (10, 38).
- d. Cortisol and growth hormone: sustain gluconeogenesis and impair insulin signaling (5, 10). Cortisol promotes hyperglycemia, which is more intense and potentiated when elevated in combination with other counter-regulatory hormones (which oppose and counteract the action of insulin), such as catecholamines. (14, 17, 39).
- e. Pro-inflammatory cytokines: Interleukin-8 (IL-8) and monocyte chemoattractant protein-1 (MCP-1) (4) especially contribute to post-burn hyperglycemia by enhancing the release of the above mentioned stress hormones and altering insulin-receptor signaling (40–42).

As can be seen, SIH is multifactorial and involves a complex cascade leading to increased hepatic output of glucose, which can be increased by about 50% in comparison to healthy controls whilst clearance is similar (10). Evidence also indicates that all insulin-counteracting hormones (epinephrine, glucagon, hydrocortisone, and growth hormone) are involved in stimulating SIH and insulin resistance (43–45).

Reduced glucose clearance

Under physiological conditions, once glucose is released, it can either be utilized by insulin independent tissues, for example in the brain, or by erythrocytes, or by insulin-dependent glucose uptake in other tissues such as muscle, or liver (46, 47). In insulin-dependant tissues, insulin binds to the α -subunit on the extracellular portion of its receptor, inducing auto-phosphorylation of the β -unit (48), leading to conformational changes and phosphorylation of insulin receptor substrate-1 (IRS-1) at a tyrosine residue, which in turn leads to activation of the phosphatidylinositol-3 kinase (PI3K)/AKT pathway (5). In key insulin-dependent tissues, such as muscle, fat, and liver, this will lead to plasma membrane localization of glucose transporter GLUT-4 (specifically and reversibly up-regulated by insulin (27)) permitting glucose uptake (10, 49) (Fig. 2). Other effects of insulin include activation of glycogen synthesis (50), lipid synthesis (51), inhibition of lipolysis (52) and lipocyte apoptosis (53), thus decreasing glucose plasma levels.

The actions of insulin normally cause a switch from catabolic breakdown and a state of gluconeogenesis and glucose release, to anabolism and a state of glucose uptake with inhibition of gluconeogenesis. Such anabolic effects are typically not seen following severe burns, where catabolic breakdown predominates. Burn patients typically present with insulin

resistance and increased proteolysis, associated with increased hepatic gluconeogenesis and muscle protein catabolism (4, 10, 54–56). These features lead to loss of lean body mass and profound muscle wasting, with consequent muscle weakness, delayed mobilization, impairment of cough reflexes, and prolonged mechanical ventilation; all of which may contribute to increased mortality in these patients (5).

Glucose clearance is diminished in burned patients as insulin-mediated uptake has been shown to be impaired when compared to normal patients (57, 58). Additional factors contributing to impaired glucose clearance include altered insulin signaling (59–61), down-regulation of genes encoding for glucose-6-phosphatase transport protein 1 gene and GLUT-4 (31). Up-regulation of the renin – angiotensin system has also been associated with insulin-resistance (62). A study of 212 severely burned children in our institution revealed that non-fasted serum glucose levels markedly increase during the acute phase post-burn to 170 to 180 mg/dL, despite concurrent raised levels of insulin. This implies the presence of insulin resistance, as seen by the observation of hyperglycemia in combination with elevated insulin levels (4).

Our knowledge of the role of cellular organelles in insulin resistance has continued to expand: the endoplasmic reticulum (ER), under conditions of cellular stress, phosphorylates the inositol requiring protein -1 (IRE-1) (63), which in turn activates c-Jun N-terminal kinase (JNK), thus leading to impaired receptor signaling by blocking tyrosine phosphorylation of the IRS-1 (64–66), features that have been observed in burn patients (5, 67, 68). Several studies have found JNK to be activated upon specific stimuli, including the presence of a number of cytokines, including IL-6, IL-8, MCP-1 and tumor necrosis factor alpha (TNF- α) (5, 10), all of which have been found to be raised under conditions known to be linked with hyperglycemia, such as obesity, diabetes mellitus and stress (69–72). The ER is not the only organelle known to be associated with SIH, as mitochondria are also believed to play an important role in the development SIH. Mitochondrial oxidation of free fatty acids (FFA) generates acetyl-CoA, reduced nicotinamide adenine dinucleotide (NADH) and adenosine 5'-triphosphate (ATP), inducing gluconeogenesis (73). Acetyl-CoA can leave the cell, becoming malonyl-CoA, activating protein kinase C which in turn inhibits insulin signaling (59, 74, 75). High levels of FFAs are observed in burns (76, 77) possibly contributing to the insulin resistance observed in these patients. Although intracellular glucose oxidation has been reported to be normal in trauma patients (30, 78), our group demonstrated that mitochondrial oxidative function is impaired in burned children by 50 – 70% at one week post-burn, persisting up to 3–4 weeks post-burn (59, 79). Furthermore, a recent study by Vanhorebeek et al. has confirmed mitochondrial dysfunction induced by hyperglycemia in an animal burn model (80). Maximal coupled mitochondrial oxidative capacity has also been shown to be severely impaired following burns, with energy production likely wasted through uncoupling (79). Improving mitochondrial function may therefore be a potential treatment target for improving insulin sensitivity, as described in patients with type-II diabetes (81).

Following the acute phase of severe burn injury, patients remain in an extreme hypermetabolic and catabolic state, with resting metabolic rate known to increase by almost 100%. This condition was in the past believed to resolve with wound closure, but has been proven to last for over a year following the time of injury (4, 5), together with elevation of counter-regulatory hormones that may perpetuate hyperglycemia. Our group has found that hyperglycemia in burned patients persists for six months after injury, but that insulin resistance may be observed for up to three years post-burn (82). The severity of this metabolic state has a length unique to burned patients. (5)

In summary, SIH following severe burns is a complex, multi-factorial condition that results from a combination of factors leading to increased glucose production and reduced uptake and clearance, with features that may persist for years after initial injury. The long term clinical relevance of SIH in burn patients is yet to be defined.

EFFECTS OF HYPERGLYCEMIA IN BURNED PATIENTS

Hyperglycemia was considered a desired condition in critically-ill patients, but recent evidence suggests significant deleterious effects of hyperglycemia. Critically-ill patients with hyperglycemia have a higher incidence of infections and sepsis in both adult and pediatric populations (10, 39, 83). In burns, patients with poor glucose control have shown poorer outcomes (17), and glucose levels higher than 200 mg/dl have been associated with a significant risk of infectious complications, especially wound infections, pneumonia and bacteremia. A glucose level greater than 140mg/dl seems to heighten the clinical suspicion for the presence of an infection in patients with burn injury (18).

Is hyperglycemia deleterious? Evidence indicates that hyperglycemia causes glycosylation of proteins, and that IgG is inactivated when glycosylated (84); it causes suppression of IL-2 and IL-10 (85) and impairs macrophage and neutrophil function. This may explain the increased incidence of infections and sepsis found in the presence of hyperglycemia. In this respect, Gore et al. found similar infection rates and hospital length of stay in burned children with poor glucose control and those with good glucose control; however they also found a statistically greater frequency of fungemia in those patients deemed hyperglycemic (13). Hyperglycemia has also been shown to impair wound healing by decreasing tensile wound strength (86), with reduced graft take in burned patients with hyperglycemia compared with those with adequate glucose control (13, 87).

The extent of the burn surface area has not been shown to correlate to mean glucose levels (17, 88), but our group has found that insulin levels were significantly increased in following >80% total body surface area burns (4). Lower levels of insulin were also observed following smaller burns, indicating that with increasing severity of burn injury, insulin resistance may increase, and more insulin needs to be synthesized to maintain normoglycemia (4).

By studying the relationship between glucose levels and mortality, it has been suggested that admission glucose levels may be a better marker for the overall initial severity of illness of the patient (9, 63, 89–91), whereas mean glucose may predict overall mortality more closely (9).

Clinical trials on hyperglycemia treatment in burned patients

The ideal target of plasma glucose to improve clinical outcome has not been determined. Van den Berghe et al. in their study showed a reduction in mortality by maintaining plasma glucose levels below 110 mg/dl (20). Holm et al. also reported improved survival when maintaining glucose in the range of 180 – 200 mg/dl (17), whilst others have suggested 120mg/dl (18), 140mg/dl (92) or 150mg/dl (93) as a desired level. The recently published Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study has assessed glucose targets using intensive-insulin control (4.5 – 6.0 mmol/L; 81–108 mg/dl) versus conventional insulin control (8.0 – 10.0 mmol/L; 144 – 180 mg/dl) in more than 6000 patients, and reported lower mortality in the conventional group (94, 95). Tables 1 and 2 provide a brief summary of clinical trials that have assessed the effects of insulin treatment in burned and mixed or non-burned patients, with varying target glucose levels.

Adequate control of hyperglycemia is not simple to achieve in burned patients: infusion of insulin when glucose levels exceeded 215 mg/dl was unsuccessful in controlling hyperglycemia in 27% of the patients in the first 48hrs after burn in one study (17). Pediatric burn patients with glucose levels above 200 mg/dl (11.1 mM/L) have been found to have poorer outcomes (13). Treatment of SIH in burned patients requires intensive insulin treatment and strict blood glucose control, in order to overcome insulin resistance, but also increases the risk of hypoglycemia (20). Intensive insulin treatment has increased severe hypoglycemic events, with incidence rates varying from 1.8% to 30%, depending on the target glucose level (96–98). Specifically in burned population, intensive insulin treatment has been shown to have either similar (18) or higher (99) rates of hypoglycemic events compared with conventional treatment. It is currently unclear whether hypoglycemia is associated with increased mortality or severe complications (i.e. seizures or death) (100). It is important to note that severely burned patients may have a potentially higher risk of hypoglycemic events, due to the requirement for frequent surgeries, daily dressing changes, and tub room visits, which also necessitate stopping of enteral feeding and can induce altered intestinal motility (2).

We should note that insulin has a wide range of effects beyond increasing cellular glucose uptake (101, 102): it has both direct and indirect immune-modulatory effects; it causes a trophic effect on mucosal and skin barriers, protecting against bacterial invasion and translocation, thus potentially decreasing infection rates (103); it improves wound matrix formation, therefore improving wound healing (104); as well as inhibiting the production of pro-inflammatory mediators (105–107) such as nuclear factor kappa B and I kappa B (108) and IL-5 and IL-6 (109).

A logical question arises as to whether the beneficial effects observed with insulin treatment are the effect of glucose modulation or is insulin *per se* responsible for them. Supporting the first premise, the hyperglycemic effects of glucose over time are known to be toxic (110, 111). Findings in surgical critically-ill patients include that death rate is correlated with the degree of hyperglycemia (for a blood glucose level of 200 mg/dL, the risk of death was found to be 2.5 times higher than for a blood glucose level of 100 mg/dL). Additionally, analysis of the observed protective effects of intensive insulin therapy on morbidity and mortality has been correlated with normalizing glucose levels, rather than with the amount of infused insulin (21, 92).

In order to test the second premise and the direct effects of insulin, a logical approach may be to use alternative drugs that cause the desired effect of decreasing plasma glucose levels, comparing the observed morbidity and mortality with expectant care and insulin treatment in a prospective, randomized and controlled protocol.

Metformin is a biguanide that effectively decreases glucose levels by improving insulin sensitivity, apparently centrally mediated (112), decreasing hepatic gluconeogenesis as much as 75% (113, 114) and has rarely been associated with hypoglycemia (5, 115). Instead, it has been associated with lactic acidosis (113), being contraindicated in hepatic or renal failure, conditions which can impair lactate clearance (116). Although a case report of metformin-related lactic acidosis in a burned patient has been published (116), in a review of trials evaluating metformin with more than 36,000 patients studied, not a single case of lactic acidosis was found, (117) indicating the low incidence of this complication when used appropriately.

Metformin not only decreases glucose levels and improves glucose clearance, but also increases the fractional synthetic rate of muscle protein, and improves net muscle protein balance (112, 118, 119), theoretically improving glucose uptake. Gore et al. performed a

randomized study in burned patients comparing metformin with placebo, and described a higher mortality in control patients (40%) than metformin treated patients (20%) (118).

Peroxisome proliferator-activated receptors (PPAR)- α agonists, such as fenofibrate, improve insulin sensitivity by improving insulin receptor signaling (increasing tyrosine phosphorylation of insulin receptor and insulin receptor substrate-1) (59) as well as by suppression of peripheral lipolysis, and redistribution of triglyceride stores to subcutaneous fat cells (59). In a double-blind, prospective, placebo-controlled, randomized trial with burned children, fenofibrate significantly improved insulin sensitivity, insulin signaling, and mitochondrial glucose oxidation (59), that can lead to a better management of SIH in burned patients (Fig 3).

Unfortunately however, improved management of hyperglycemia has not been adequate with metformin or fenofibrate alone, with the addition of insulin needed to achieve the target glucose levels cited in the protocols, and making difficult to categorically conclude if insulin or glucose modulation are responsible for the effects in burned patients.

DISCUSSION

Stress-induced hyperglycemia is a multi-factorial condition, and is a complex process in severely burned patients. The incidence and prevalence of hyperglycemia in burned patients is difficult to determine, and this review has found that at present, there is as yet no consensus on a glucose level that defines hyperglycemia or a safe target glucose range for treatment in burned patients. It should be taken into consideration that by defining hyperglycemia at a level higher than 110mg/dl, which is the consensus in other patients, would imply that higher glucose levels are normal or acceptable in burned patients. The glucose level used to define hyperglycemia does not necessarily have to be the same as the target glucose range used for therapy.

The studies described in this article have found an increased incidence of fungemia, bacterial infections, and sepsis in hyperglycemic patients. These conditions themselves can produce or perpetuate hyperglycemia, indicating that hyperglycemia may also be a marker of sepsis rather than a direct cause. The fact that diabetic patients have an increased incidence of infection, and that impairment occurs of immune cells, immunoglobulins, and inflammatory mediators *in vitro* when exposed to high glucose levels (84, 85) supports the role of hyperglycemia in increasing the incidence of infection. Furthermore, by treating hyperglycemia, infection rates are decreased, resulting in a beneficial impact on mortality, as infection and sepsis are major causes of death in severely burned patients (13, 120). Length of stay (LOS) has also been found to be increased in critically-ill patients with hyperglycemia (9), although this has not been found specifically among burned patients (13, 18, 99).

Insulin has both anabolic and anti-inflammatory effects as previously described, making it unlikely that the beneficial effects observed with intensive insulin treatment result only from normalization of glucose levels, being rather the combination of both glucose modulation and insulin action to some degree.

Interesting findings from a recent study in healthy individuals reported the effect of insulin following glucose ingestion, and indicated that some humans are selectively resistant to insulin's suppression of proteolysis, whereas others to insulin's suppression of lipolysis, which potentially leads to an "insulin response profile" (55). This finding may provide an explanation of the different responses to insulin observed even within the same study (112).

Regarding cytokines and interleukins, although IL-6 is elevated in burned patients, it has not been found to be a contributor to acute hyperglycemia induced by stress (121). Similarly, IL-1 has not been associated with hyperglycemia in burn patients. In fact, it has been described that an IL-1 β -secreting tumor increased glucose uptake and decreased hepatic gluconeogenesis, leading to the development of hypoglycemia (122). Additionally, hyperglycemia itself may lead to an increased concentration of circulating cytokines, including IL-6 (123).

In the NICE – SUGAR study, survival was found to be better in the conventional group, but further analysis of the odds ratio for death (95% CI), resulted in better outcome within the trauma subpopulation with intensive insulin treatment (95). Unfortunately, it was not described if burn patients were included in the study.

The utility of alternative anti-hyperglycemic drugs in order to decrease the incidence of hypoglycemic events observed with insulin is still under study. The decreased mortality rates described by Gore et al. using metformin in burned patients (118), which included only 5 patients per group, included a death in the placebo group secondary to dislodgement of an endotracheal tube, making it difficult to achieve a conclusion in this study. The literature on the use of metformin in burned patients remains scarce.

It is likely that decreasing glucose levels with intensive insulin therapy may be beneficial in critically-ill patients, but the current evidence is not decisive, especially for burned patients. Although the available studies have shown improved survival with lower glucose levels, the studied population is small, with the studies being either retrospective or not controlled. It is yet to be determined whether insulin or euglycemia would be responsible for the mentioned effects.

A table of up-to date clinical trials studying hyperglycemia in burned patients (Table 1) has been compiled, but based on this review, we can conclude that an ideal target range for glucose levels in burned patients is still to be determined.

FUTURE DIRECTIONS

With recent multi-center trials indicating potential harm from intensive-insulin treatment, while others indicate beneficial outcomes, the future of tight glycemic control remains intriguing. Several key questions remain to be addressed, for example, which patient populations is tight euglycemic control most beneficial? Current evidence indicates possible advantages in the use of intensive-insulin regimens during the acute management of trauma patients (Van den Berghe et al (20–22), Pham et al (99)) recently confirmed in a sub-analysis of the published NICE – SUGAR trial (95).

In severely burned patients, effects and implications of euglycemic control following injury remains to be determined, and groups including our own are currently conducting trials to clarify this issue. Another important factor for this population would be to determine an effective yet safe glucose range for optimal outcomes.

Debate also persists as to whether the findings described arise due to insulin treatment, from modulation of glucose levels, or a combined effect. Newer generations of anti-hyperglycemic drugs may help to clarify whether glucose-modulation leads to the suggested benefits. These include the PPAR-modulators fenofibrate and glitazones, as well as glucagon-like peptide-1 (GLP-1) and its analogues and dipeptidyl peptidase-4 (DDP-4) inhibitors. However, the role and efficacy of these agents in the trauma and burn care setting is yet to be evaluated.

The duration of hyperglycemia and altered insulin sensitivity following burn injury is a recent finding made by our group. Hyperglycemia was shown to persist for six months, while insulin sensitivity remained disturbed for a striking duration of up to three years post-burn (82). Long-term follow up studies would be useful in assessing the clinical impact of the prolonged disturbance in glucose kinetics in burn survivors. This would also help to determine whether patients may benefit from interventions to treat altered insulin sensitivity and glucose kinetics after discharge.

We suggest that an evidence-based consensus is needed on an appropriate and safe target range for glucose levels during acute burn care. A multi-center study may be required to accomplish this in order to enroll the number of patients required to reach an unequivocal conclusion. Controversy and debate is welcome, as when tackled constructively, leads to progress through innovation and novel approaches, and results in enhanced treatment strategies and patient care.

CONCLUSION

Although most burn centers may be implementing intensive insulin practices, the available literature fails to unequivocally confirm superior risk-benefit ratio of intensive insulin treatment in these patients. Severely burned patients represent the most critical trauma model, necessitating prospective, randomized and controlled studies to assess the impact of hyperglycemia and its treatment specifically in burned patients. It is likely that multi-center studies will be needed to collect enough information to be able to produce a consensus that will determine the paradigm of treatment of hyperglycemia in burned patients.

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Fig. 1.

Determination of glucose concentration in plasma. A. Plasma glucose levels are determined by production/external load and uptake of glucose from peripheral tissues. B. An increased production/load, decreased uptake or both causes increased glucose levels.

Fig. 2.

Insulin independent tissues (i.e. erythrocyte) do not require insulin to uptake glucose. Insulin-dependent tissues require insulin binding to insulin receptor to activate the insulin signaling, leading to expression of the GLUT-4 transporter permitting glucose uptake and further oxidation by mitochondria.

Fig. 3.

Burned patients typically had impaired insulin signaling, decreasing insulin uptake by the cells, and affecting the mitochondrial oxidation. Metformin primarily acts by reducing hepatic glucose production. Fenofibrate attenuates insulin resistance by acting in the insulin signaling, and increasing mitochondrial oxidation of intracellular glucose. Metformin decreases hepatic gluconeogenesis and improves insulin sensitivity.

Table 1
Compilation of studies on burned patients describing the morbidity and mortality according to the target plasma glucose levels (PGL).

Burned Patients									
Author	Number of Patients	Target or Studied Glucose Level	LOS (days)	Wound Infection	Bacterial Infection	Fungemia	Graft Take	Mortality	Comments
Gore et al (13).	Normo=25 Hyperg=33	7.8mm/L	No difference *	No difference *	No difference *	Higher with hyperg	/ Normo= 88% Hyperg= 64%	/ Normo= 4% Hyperg= 27%	Retrospective study
Holm et al (17).	78	180–200 mg/dl	ND	ND	ND	ND	ND	/ Higher with hyperglycemia	Studied mean glucose levels depending on survival
Hemmila et al (18).	Normo=71 Hyperg=81	140 mg/dl	No difference *	ND	/ Normo= 16% Hyperg= 37%	ND	ND	No difference *	
Pham et al (99).	Normo=33 Hyperg=31	<200mg/dl	No difference *	ND	ND	ND	ND	/ Normo= 0% Hyperg= 75%	Retrospective study

Normo: patients with PGL below the target. Hyperg: patients with PGL above the target. LOS: Length of stay. ND: Not described in the article.

* No significant difference.

/ Statistically significant ($p < 0.05$).

Table 2

Compilation of studies on trauma and non trauma patients describing the morbidity and mortality according to the target plasma glucose levels (PGL).

Trauma and Non Trauma Patients							
Author	Number of Patients	Target or Studied Glucose Level	LOS (days)	Wound Infection	Bacterial Infection	Mortality	Comments
Wahl et al (9).	531	140 mg/dl	ND	ND	ND	<i>I</i> Normo= 11% Hyperg= 40%	Burn patients were excluded
Van den Berghe et al (20).	Normo= 765 Hyperg= 783	80–110 mg/dl	ND	ND	<i>I</i> Normo= 4.2% Hyperg= 07.8%	<i>I</i> Normo= 07.2% Hyperg= 10.9%	Surgical ICU
Van den Berghe et al (20).	Normo= 4/33 Hyperg= 3/35	80–110 mg/dl	ND	ND	ND	<i>I</i> Normo= 08.6% Hyperg= 12.1%	Burned/trauma sub-population
Van den Berghe et al (22).	Normo= 605 Hyperg= 595	80–110 mg/dl	ND	ND	ND	No difference *	Medical ICU
Shin et al (63).	Normo= 319 Hyperg= 290	150 mg/dl	No difference *	ND	<i>I</i> Normo= 27.6% Hyperg= 43.2%	<i>I</i> Normo= 08.2% Hyperg= 18.5%	Retrospective study
Tuggle et al (83).	Normo= 09 Hyperg= 48	130 mg/dl	Increased with hyperglycemia	<i>I</i> Normo= 00% Hyperg= 33%	ND	ND	Burn patients were excluded
NICE-SUGAR study investigators (95).	Conv= 3014 Int = 3016	Conv= <180 mg/dl Int= 81–108 mg/dl	No difference *	ND	ND	<i>I</i> Conv= 24.9% Int= 27.5%	Mortality significant at day 90
NICE-SUGAR study investigators (95).	Conv= 465 Int = 421	Conv= <180 mg/dl Int= 81–108 mg/dl	ND	ND	ND	[†] Conv= 41/421 Int= 57/465	Trauma sub-population
Krinsley et al (97).	Normo= 800 Hyperg= 800	140 mg/dl	No difference *	ND	No difference *	<i>I</i> Normo= 14.8% Hyperg= 20.9%	Historic controls
Quinn et al (124).	Normo= 70 Hyperg= 143	91–130 mg/dl	No difference *	ND	ND	No difference *	No burn patients. Retrospective study

Normo: patients with PGL below the target. Hyperg: patients with PGL above the target. Conv: Conventional treatment group. Int: Intensive treatment group. LOS: Length of stay. ND: Not described in the article. ICU: Intensive Care unit.

* Not significant difference.

I Statistically significant ($p < 0.05$).

[†] Odds ratio for death (95% CI): 0.77 (0.50–1.18)