Published in final edited form as:

Burns. 2014 May ; 40(3): 428–435. doi:10.1016/j.burns.2013.07.007.

Bacterial Respiratory Tract Infections are Promoted by Systemic Hyperglycemia after Severe Burn Injury in Pediatric Patients

Robert Kraft^e, David N Herndon^{b,c}, Ronald P Mlcak^b, Celeste C Finnerty^{b,c,d}, Robert A Cox^b, Felicia N Williams^b, and Marc G Jeschke^a

^aRoss Tilley Burn Centre, Sunnybrook Health Sciences Centre, Sunnybrook Research Institute, Department of Surgery, Immunology, and Division of Plastic Surgery, University of Toronto, Toronto, Canada

^bShriners Hospitals for Children, Galveston, Texas

^cDepartment of Surgery, University Texas Medical Branch, Galveston, Texas

^dSealy Center for Molecular Medicine, and the Institute for Translational Science, University Texas Medical Branch, Galveston, Texas

^eDepartment of Trauma, Klinikum Memmingen, Germany

Abstract

Background—Burn injuries are associated with hyperglycemia leading to increased incidence of infections with pneumonia being one of the most prominent and adverse complication. Recently, various studies in critically ill patients indicated that increased pulmonary glucose levels with airway/blood glucose threshold over 150 mg/dl lead to an overwhelming growth of bacteria in the broncho-pulmonary system, subsequently resulting in an increased risk of pulmonary infections. The aim of the present study was to determine whether a similar cutoff value exists for severely burned pediatric patients.

Methods—One-hundred six severely burned pediatric patients were enrolled in the study. Patients were divided in two groups: high (H) defined as daily average glucose levels >75% of LOS >150 mg/dl), and low (L) with daily average glucose levels >75% of the LOS <150 mg/dl). Incidences of pneumonia, atelectasis, and acute respiratory distress syndrome (ARDS) were assessed. Incidence of infections, sepsis, and respiratory parameters were recorded. Blood was

© 2013 Elsevier Ltd and ISBI. All rights reserved.

Corresponding author: Marc G. Jeschke, MD, PhD, FACS, Ross Tilley Burn Centre, Sunnybrook Health Sciences Centre, University of Toronto, 2075 Bayview Avenue, Room D704, Toronto, ON, Canada M4N 3M5; Tel.:416-480-6703; Fax 416-480-6763; marc.jeschke@sunnybrook.ca.

Author Contributions

The study was designed by RK, DNH, RPM, MGJ. Acquisition of data was performed by RK, DNH, RPM, MGJ. Analysis and interpretation of data was done by RK, DNH, RAC, CCF, FNW, RPM, MGJ. The manuscript was drafted by RK, MGJ. Critical revision of the manuscript for important intellectual content was done by RK, DNH, RAC, CCF, MGJ. The statistical analysis was done by RK, MGJ. Final approval of the manuscript was done by RK, DNH, RAC, RPM, FNW, MGJ. All authors had access to the data and taking responsibility for the integrity and the accuracy of the data analysis.

CONFLICT OF INTEREST

None of the authors has any financial, professional or personal relationships with other people or organizations that could be construed as influencing (bias) this work.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

analyzed for glucose and insulin levels. Statistical analysis was performed using Student's t-test and chi-square test. Significance was set at $p < 0.05$.

Results—Patient groups were similar in demographics and injury characteristics. Pneumonia in patients on the mechanical ventilation (L: 21% H: 32%) and off mechanical ventilation (L: 5% H: 15%), as well as ARDS were significantly higher in the high group (L: 3% H: 19%), $p < 0.05$, while atelectasis was not different. Patients in the high group required significantly longer ventilation compared to low patients ($p < 0.05$). Furthermore, incidence of infection and sepsis were significantly higher in the high group, $p < 0.05$.

Conclusion—Our results indicate that systemic glucose levels over 150 mg/dl are associated with a higher incidence of pneumonia confirming the previous studies in critically ill patients.

Keywords

Pneumonia; respiratory tract infections; bacterial growth; airway glucose threshold; hyperglycemia

INTRODUCTION

Critically ill patients and especially burn patients are at a high risk for infectious complications [1]. Severe infections are one of the leading cause in burn patients resulting in prolonged hospitalization [2, 3] and worsened outcome [2]. One of the major infectious complications is pneumonia, which has been shown to increase burn mortality by 40% [4, 5]. On the hand, severe thermally injured patients are particularly at risk for the development of pneumonia because of their vast hypermetabolic and inflammatory response, profound immune compromise, prolonged bed rest, and need for mechanical ventilation [2]. Ventilation leads to impaired mucociliary clearance and excretion of pathogens with increased mucus content in the airways [6, 7]. Not only does the amount of mucus affects infections, but it has also been shown in an in vitro experiment that increased glucose content in media promotes the bacterial growth [7–9]. Under physiologic conditions, glucose is not detectable in the airway fluids [10]. In a recent study, it was shown that systemic blood glucose levels greater than 8 mmol/l (144 mg/dl) lead to a marked increased glucose content in the airway system [11]. Increased glucose concentration in the mucus presents an excellent media for bacteria such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* [12].

As aforementioned, a hallmark after severe burn injury is hypermetabolism associated with hyperglycemia and insulin resistance [13, 14]. Increased pulmonary glucose levels with an airway/blood glucose threshold over 150 mg/dl lead to an overwhelming growth of bacteria in the broncho-pulmonary system, leading to increased risks of pulmonary infections [12]. Therefore, we determined whether this airway/blood glucose threshold can be translated to burn patients. The aim of this study was to determine whether systemic glucose levels over 150 mg/dl lead to increased pneumonia and pulmonary complications indicating bacterial growth promotion caused by the an existing airway glucose threshold.

PATIENTS AND METHODS

This cohort study used two-hundred eight severely burned pediatric (ages 0–17) patients with burns over 30% total burn surface area (TBSA). All individuals participated in a prospective randomized trial determining who consented to an IRB-approved experimental protocol between 2002 and 2008 determining the effects of tight glycemic control after severe burn injury were included in this study. Patients considered being futile at admission were excluded from the study. Patients were evaluated for their glycemic control according

to their systemic glucose levels in responders and non-responders according the following criteria. A cut-off value of 150 mg/dl systemic blood glucose was used for the assessment of the success of glycemic control. Patients with good glucose control (at least for 75% of the length of stay below 150 mg/dl) were assigned to the low-glucose level group (L). All other subjects were stratified to the group with high glucose levels (H). A subset of 106 patients with continuous chest radiographic evaluation of the incidence of pneumonia was analyzed according to the incidence of pneumonia, atelectasis, and acute respiratory distress syndrome (ARDS) during the ICU stay. Furthermore, we determined the ratio of arterial partial oxygen pressure and fraction of inspired oxygen (P/F ratio), length of ventilation, and positive end expiratory pressures (PEEP). Lastly, burn wound infection and sepsis was prospectively determined.

At admission, patients received standardized burn care [15]. Patients were resuscitated according to the Galveston formula with 5000 cc/m² TBSA burned + 2000 cc/m² TBSA lactated Ringer's solution given in increments over the first 24 hours as necessary. Within 48 hours of admission, all patients underwent total burn wound excision and their wounds were covered with autograft. Any remaining open areas were covered with homograft. After the first operative procedure, patients were taken back to the operation theater when donor sites were healed. This procedure was repeated until all open wound areas were covered with autologous skin. All patients underwent the same nutritional treatment according to a standardized protocol. Intake was calculated as 1500 kcal/m² body surface + 1500 kcal/m² area burn as previously described [16–18]. The nutritional route of choice in our patient population was enteral nutrition via a naso-duodenal (Dobhoff) or nasogastric tube. Parenteral nutrition was only given in rare instances if the patient could not tolerate tube feeds. All patients received an antibiotic regimen at admission consisting of Vancomycin, Pip/Tazo and Fluconazole. There was no difference between groups in the antibiotic regimen.

Patient demographics (age, date of burn and admission, sex, burn size and depth of burn), concomitant injuries such as inhalation injury, and outcomes (sepsis, morbidity, and mortality) were recorded. Inhalation injury was diagnosed by bronchoscopy along with a consistent history. Wound infection was defined as >10⁵ colony forming units per gram tissue in a wound biopsy with the identification of a pathogen [19]. Repeated counts of the same bacteria in the same location were counted as the same infection. Sepsis and infection were diagnosed in accordance with the American Burn Association and Society of Critical Care Medicine guidelines. Sepsis and infection were defined by the American Burn Association and Society of Critical Care Medicine guidelines [20, 21]. Sepsis was defined as a positive blood culture or pathologic tissue identifying the pathogen during hospitalization or at autopsy, in combination with at least three of the following: leucocytosis or leucopenia (>12,000 or <4,000/μl), hyperthermia or hypothermia (>38.5 or <36.5°C), tachycardia (>20% above normal value), refractory hypotension (systolic BP <20% below normal value), thrombocytopenia (platelets <50,000/mm³), hyperglycemia (serum glucose >240 mg/dl), and enteral feeding intolerance (residuals > 200 cc/hr or diarrhea >1 L/day) according the modified ACCP/SCCM criteria [20, 21]. We further determined time between operations as a measure for wound healing and re-epithelization. Patient data was collected prospectively using the clinical information system Emtex by physicians, nurses and supportive staff. Data was processed and analyzed with Microsoft Access 2007®, Excel 2007®, Microsoft Corporation Inc. (Redmond, WA, USA).

Definitions

Pneumonia—The clinical diagnosis of pneumonia included the following:

- a. Chest x-ray revealing a new or persistent infiltrate, consolidation, or cavitation.

- b. A recent change in sputum or purulence in the sputum.
- c. Tracheal aspirate 10^5 organisms.
- d. Bronchoalveolar lavage (BAL): 10^4 organisms.

Adult Respiratory Distress Syndrome (ARDS)—The definition of the syndrome include patients who met the following criteria:

- a. Acute onset.
- b. Pulmonary artery wedge pressure <18 mmHg or absence of clinical evidence of left atrial hypertension.
- c. Bilateral infiltrates on chest radiography.
- d. $\text{PaO}_2/\text{FiO}_2$ ratio (P/F) ≤ 200 .

Radiographic imaging

Chest X-ray were evaluated by the attending physician and independently interpreted by the attending radiologist and stratified according the incidence of pneumonia, atelectasis, and ARDS.

Respiratory parameters

Duration of mechanical ventilation and levels of positive end expiratory pressure (PEEP) were obtained from the patients' charts. Ventilated patients received a daily sedation vacation and a spontaneous breathing trial and were extubated according to protocol.

Hormones and proteins

Blood was collected from burn patients at admission and up to 60 days post injury for protein analysis. Blood was drawn in a serum-separator collection tube and centrifuged for 10 minutes at 1320 rpm; the serum was removed and stored at -70°C until assayed. Serum insulin, C-reactive protein (CRP), and retinol binding protein (RBP) were determined using HPLC [22], nephelometry (BNII, Plasma Protein Analyzer Dade Behring, MD), and ELISA techniques.

Ethics and statistics

The study was reviewed and approved by the Institutional Review Board of the University Texas Medical Branch, Galveston, Texas. Prior to the study, each subject, parent or child's legal guardian signed a written informed consent form. For biochemical measurements, we applied the Confidence Interval 2σ ($\text{CI} = 0.9544997$) to improve reliability. Unpaired Student's t-test, Chi-square analysis, linear and logistic regression analysis and Mann-Whitney tests were used as appropriate. Statistical analysis was performed using Microsoft Excel® and Systat Software Sigmaplot® version 3.5 and Sigmaplot®, Systat Software Inc. (San Jose, CA, USA). Data are expressed as means $\pm$ SD or SEM, where appropriate. Significance was accepted at $p < 0.05$. Participating patients were part of a clinical trial registered at www.clinicaltrials.gov/NCT00673309.

RESULTS

Demographics and clinical outcome

Patient demographics are shown in Table 1. Both groups are similar in ethnicity and gender distribution. The high-glucose group was on average five years older ($p < 0.05$) than the low-glucose group. The severity of injury (%TBSA total, 3rd and incidence of inhalation injury)

was similar in both groups. High-glucose patients demonstrated a significantly higher incidence of sepsis and infections compared to the low glucose group, $p<0.05$. Increased incidence of infection and sepsis was associated with an increased mortality in the high glucose group, $p<0.05$ (Table 2).

Glucose levels and insulin requirements

Daily average glucose levels were consistently over the determined threshold of 150 mg/dl during the first 30 days in the H group with a significant ($p<0.05$) different AUC between both groups (Figure 1). The low-glucose group was under this cut off during the whole study period. Insulin requirements are shown in Figure 2. The group with higher systemic glucose levels required significantly ($p<0.05$) more insulin (2A) with a less response resulting in significantly ($p<0.05$) higher glucose levels (2B) indicating profound insulin resistance.

Incidence of pneumonia, atelectasis and ARDS

Analysis regarding the incidence of pneumonia shows a significant ($p<0.05$) higher incidence of pneumonia in patients on and off mechanical ventilation and ARDS (Table 3) in the group with glucose levels higher than 150 mg/dl. The incidence of atelectasis was not significantly different between groups (Table 3).

Respiratory parameters

Patients with high-average glucose levels required ventilation significantly longer (10 days) with a significant higher maximum PEEP (11 ± 4 mmHg) compared to low-glucose patients (3 ± 2 days, 6 ± 2 mmHg) ($p<0.05$). P/F ratio did not show significant differences during the first 72 hours after admission between the groups showing consistency in lung function between both groups at admission.

Biomarkers

C-reactive protein (CRP) (Figure 3A) as an established inflammatory marker was significantly ($p<0.05$) elevated in the group over 150 mg/dl, $p<0.05$. Retinol binding protein (RBP) (Figure 3B) followed this pattern, which was significantly elevated in the high group ($p<0.05$).

DISCUSSION

The beneficial effect of tight euglycemic control in critically ill patients has been shown in several clinical trials [23–26]. However, other clinical trials exist that didn't observe beneficial outcomes. In contrast, these trials found tight euglycemic control to be dangerous and associated with worsened outcomes [27]. Therefore, the current recommendation according to Finfer et al. [28] and Preiser et al. [29] as well as the Sepsis guidelines are to achieve intermediate systemic glucose levels of 140 mg/dl [27]. The hypothesis behind this recommendation is to alleviate hyperglycemia, which is detrimental, and also to avoid hypoglycemia but still achieve beneficial effects of glucose control. Our present study followed this guideline by choosing a cut-off level above 150 mg/dl where glucose can be found in the airway surface layers [12]. This is important as we have recently shown that a 6-am glucose level of 130 mg/dl or a daily average of 140 mg/dl is associated with improved morbidity and mortality after burn [30]. However, the chosen threshold is not in accordance with the current recommendations for the treatment of sepsis and septic shock in critically ill patients target higher glucose levels [31]. In our present study, we examined the organ specific impact under the aspect of infections on lung tissue.

Regarding the study aim, we found that systemic hyperglycemia with levels over 150 mg/dl are associated with significantly increased postburn pulmonary complications. Our data

reveal that patients with average glucose levels below 150 mg/dl showed a significant lower incidence of sepsis, infectious complications, pulmonary complications, and mortality. These results are conforming to other clinical studies. We and others [2, 32, 33] hypothesize that one of the reasons for an increased postburn morbidity and mortality is an increased inflammatory and acute phase response. Our results confirm this hypothesis by significantly elevated acute phase protein CRP and RBP plasma levels in the high glucose group. Serum RBP is also suggested being associated with insulin resistance and hyperglycemia besides as being a marker for inflammatory processes [34]. It correlates accordingly in our study with the finding of higher glucose levels combined with higher insulin requirements in the high-glucose group. Several studies suggest that protein glycolysation is one of the pathophysiologic responses occurring at glucose levels over 150 mg/dl [10, 35] that might contribute to the worsened outcome in the high group.

Nevertheless, the most important finding of the present study was the significant higher incidence of infectious complications of the lung in the group with glucose levels over 150 mg/dl. Our study attempted to show that systemic glucose levels promote the incidence of pulmonary bacterial infections by mucus glucose concentration. We did not measure airway surface layer glucose concentration in our burn patients, but Brennan et al. [36] demonstrated elegantly that mucus glucose is detectable and increased once systemic glucose reaches a concentration over 8 mmol/l. We, therefore, suggest that a direct effect of glucose as a promoting factor for bacterial growth exists, leading to an increased incidence of airway infections. We found not only that pneumonia is increased, but also ARDS and lung mechanics are significantly worse in the high-glucose group. Whether pneumonia causes an increased need for ventilation and ARDS, or whether ventilation and ARDS lead to an increased incidence of pneumonia is unclear; but our data shows clearly that systemic high glucose levels are linked with a significantly higher incidence of pneumonia in the critical ill patient. Additionally, hospital stay, morbidity, and mortality were clearly affected and significantly worse in the high-glucose group.

In terms of mechanisms by which high airway glucose levels cause bacterial growth, we believe that glucose influences the bacterial load as a metabolic substrate [36] and in higher concentration in the setting of altered mucociliary clearance [7]. Presence of glucose leads to a higher viscosity and is a osmotic active molecule causing a shift of fluid through the lung tissue [9, 35]. As a result, mucociliary clearance is reduced and the excretion of pathogens is impaired. Interestingly, one would expect that higher mucus viscosity leads to increased atelectasis, but this was not the case. We did not find any difference between both groups.

A limitation of this study that has to be addressed is the lack of airway glucose level measurements. Therefore, it has to be annotated that obtaining these measurements, especially from the deeper airways, is only possible by a bronchoscopic procedure. Other studies in healthy volunteers utilized the glucose levels in nasal secretions [10]. The validity of these surrogate measurements would also be problematic in critical ill patients due to inserted nasal gastric tubes which possibly could contaminate the nasal surface with glucose containing medications or food. Another limitation is that this study was using the envelope of a prior prospective clinical trial and setup as its own prospective trial limiting interventions, patients, non-responders, and mechanisms.

Despite these points from critics, the present study demonstrated that systemic high glucose levels have a significant relationship to bacterial growth in lung tissue represented by the incidence of pneumonia. These results might be attributable to the aforementioned mechanisms of the glucose airway threshold. To confirm the casual underlying mechanisms, more mechanistic research in hyperglycemic patients needs to be done. We suggest the direct effect of glucose as a growth media for bacteria combined with altered mucus

viscosity as main contributors to the development of pneumonia in hyperglycemic critically ill patients. Extended mechanistic investigation of the presented results might significantly contribute to the understanding of the beneficial effects of targeted glucose control in the ICU. This study supports our hypothesis that the ideal blood glucose should be around 130–140 mg/dl in severely burned patients.

Acknowledgments

The authors thank all the individuals who participated in this clinical trial. This study was supported by grants from Shriners Hospitals for Children (71008, and 79135), National Institutes of Health (R01-GM56687, T32-GM008256, P50-GM60338, and R01-GM087285-01), and National Institute on Disability and Rehabilitation Research (H133A020102), Canadian Institutes of Health Research (123336), and Physician's Services Incorporated Foundation: Health Research Grant Program.

The sponsors had no role in the design or conduct of the study, in the collection, analysis, or interpretation of data, or in the preparation, review, or approval of the manuscript.

References

1. Takahashi H, Tsuda Y, Takeuchi D, Kobayashi M, Herndon DN, Suzuki F. Influence of systemic inflammatory response syndrome on host resistance against bacterial infections. *Crit Care Med*. 2004; 32:1879–85. [PubMed: 15343016]
2. Jeschke MG, Chinkes DL, Finnerty CC, Kulp G, Suman OE, Norbury WB, et al. Pathophysiologic response to severe burn injury. *Ann Surg*. 2008; 248:387–401. [PubMed: 18791359]
3. Xiao-Wu W, Herndon DN, Spies M, Sanford AP, Wolf SE. Effects of delayed wound excision and grafting in severely burned children. *Arch Surg*. 2002; 137:1049–54. [PubMed: 12215159]
4. Mlcak RP, Suman OE, Herndon DN. Respiratory management of inhalation injury. *Burns*. 2007; 33:2–13. [PubMed: 17223484]
5. Church D, Elsayed S, Reid O, Winston B, Lindsay R. Burn wound infections. *Clin Microbiol Rev*. 2006; 19:403–34. [PubMed: 16614255]
6. Mathews PJ, Mathews LM. Reducing the risks of ventilator-associated infections. *Dimens Crit Care Nurs*. 2000; 19:17–21. [PubMed: 10876481]
7. Cox RA, Mlcak RP, Chinkes DL, Jacob S, Enkhbaatar P, Jaso J, et al. Upper airway mucus deposition in lung tissue of burn trauma victims. *Shock*. 2008; 29:356–61. [PubMed: 17693942]
8. Murakami K, McGuire R, Cox RA, Jodoin JM, Schmalstieg FC, Traber LD, et al. Recombinant antithrombin attenuates pulmonary inflammation following smoke inhalation and pneumonia in sheep. *Crit Care Med*. 2003; 31:577–83. [PubMed: 12576969]
9. Kalsi KK, Baker EH, Fraser O, Chung YL, Mace OJ, Tarelli E, et al. Glucose homeostasis across human airway epithelial cell monolayers: role of diffusion, transport and metabolism. *Pflugers Arch*. 2009; 457:1061–70. [PubMed: 18781323]
10. Wood DM, Brennan AL, Philips BJ, Baker EH. Effect of hyperglycaemia on glucose concentration of human nasal secretions. *Clin Sci (Lond)*. 2004; 106:527–33. [PubMed: 14678009]
11. Philips BJ, Meguer JX, Redman J, Baker EH. Factors determining the appearance of glucose in upper and lower respiratory tract secretions. *Intensive Care Med*. 2003; 29:2204–10. [PubMed: 14647890]
12. Philips BJ, Redman J, Brennan A, Wood D, Holliman R, Baines D, et al. Glucose in bronchial aspirates increases the risk of respiratory MRSA in intubated patients. *Thorax*. 2005; 60:761–4. [PubMed: 16135681]
13. Herndon DN, Hart DW, Wolf SE, Chinkes DL, Wolfe RR. Reversal of catabolism by beta-blockade after severe burns. *N Engl J Med*. 2001; 345:1223–9. [PubMed: 11680441]
14. Jeschke MG, Mlcak RP, Finnerty CC, Norbury WB, Gauglitz GG, Kulp GA, et al. Burn size determines the inflammatory and hypermetabolic response. *Crit Care*. 2007; 11:R90. [PubMed: 17716366]

15. Branski LK, Mittermayr R, Herndon DN, Norbury WB, Masters OE, Hofmann M, et al. A porcine model of full-thickness burn, excision and skin autografting. *Burns*. 2008; 34:1119–27. [PubMed: 18617332]
16. Hart DW, Wolf SE, Chinkes DL, Gore DC, Mlcak RP, Beauford RB, et al. Determinants of skeletal muscle catabolism after severe burn. *Ann Surg*. 2000; 232:455–65. [PubMed: 10998644]
17. Hart DW, Wolf SE, Mlcak R, Chinkes DL, Ramzy PI, Obeng MK, et al. Persistence of muscle catabolism after severe burn. *Surgery*. 2000; 128:312–9. [PubMed: 10923010]
18. Mlcak RP, Jeschke MG, Barrow RE, Herndon DN. The influence of age and gender on resting energy expenditure in severely burned children. *Ann Surg*. 2006; 244:121–30. [PubMed: 16794397]
19. Gallagher, JJ.; Branski, LK.; Williams-Bouyer, N.; Villarreal, C.; Herndon, DN. Treatment of infection in burns. In: Herndon, DN., editor. *Total Burn Care*. 4. China: Saunderson-Elsevier; 2012. p. 137–56.
20. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med*. 2003; 31:1250–6. [PubMed: 12682500]
21. Bone RC, Sibbald WJ, Sprung CL. The ACCP-SCCM consensus conference on sepsis and organ failure. *Chest*. 1992; 101:1481–3. [PubMed: 1600757]
22. Jeschke MG, Finnerty CC, Suman OE, Kulp G, Mlcak RP, Herndon DN. The effect of oxandrolone on the endocrinologic, inflammatory, and hypermetabolic responses during the acute phase postburn. *Ann Surg*. 2007; 246:351–62. [PubMed: 17717439]
23. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med*. 2006; 354:449–61. [PubMed: 16452557]
24. Wu X, Thomas SJ, Herndon DN, Sanford AP, Wolf SE. Insulin decreases hepatic acute phase protein levels in severely burned children. *Surgery*. 2004; 135:196–202. [PubMed: 14739855]
25. Jeschke MG, Klein D, Herndon DN. Insulin treatment improves the systemic inflammatory reaction to severe trauma. *Ann Surg*. 2004; 239:553–60. [PubMed: 15024317]
26. Pierre EJ, Barrow RE, Hawkins HK, Nguyen TT, Sakurai Y, Desai M, et al. Effects of insulin on wound healing. *J Trauma*. 1998; 44:342–5. [PubMed: 9498508]
27. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med*. 2008; 358:125–39. [PubMed: 18184958]
28. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009; 360:1283–97. [PubMed: 19318384]
29. Preiser JC, Devos P, Ruiz-Santana S, Melot C, Annane D, Groeneveld J, et al. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive Care Med*. 2009; 35:1738–48. [PubMed: 19636533]
30. Jeschke MG, Kraft R, Emdad F, Kulp GA, Williams FN, Herndon DN. Glucose control in severely thermally injured pediatric patients: what glucose range should be the target? *Ann Surg*. 2010; 252:521–8. [PubMed: 20739853]
31. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Crit Care Med*. 2013; 41:580–637. [PubMed: 23353941]
32. Cree MG, Fram RY, Barr D, Chinkes D, Wolfe RR, Herndon DN. Insulin resistance, secretion and breakdown are increased 9 months following severe burn injury. *Burns*. 2009; 35:63–9. [PubMed: 18672331]
33. Hotamisligil GS. Inflammatory pathways and insulin action. *Int J Obes Relat Metab Disord*. 2003; 27 (Suppl 3):S53–5. [PubMed: 14704746]
34. Yao-Borengasser A, Varma V, Bodles AM, Rasouli N, Phanavanh B, Lee MJ, et al. Retinol binding protein 4 expression in humans: relationship to insulin resistance, inflammation, and response to pioglitazone. *J Clin Endocrinol Metab*. 2007; 92:2590–7. [PubMed: 17595259]
35. Saumon G, Martet G, Loiseau P. Glucose transport and equilibrium across alveolar-airway barrier of rat. *Am J Physiol*. 1996; 270:L183–90. [PubMed: 8779986]

36. Brennan AL, Gyi KM, Wood DM, Johnson J, Holliman R, Baines DL, et al. Airway glucose concentrations and effect on growth of respiratory pathogens in cystic fibrosis. *J Cyst Fibros*. 2007; 6:101–9. [PubMed: 16844431]

Figure 1.
Average daily glucose levels during the hospital stay.

Figure 2.
 Plasma insulin and glucose levels.

Figure 3.
Biomarkers and mediators of the inflammatory response. Abbr.: CRP = C Reactive Protein, RBP= Retinol Binding Protein, MCP-1= Monocyte Chemoattractant Protein 1, IL-6 = Interleukin 6.

Table 1

Patients' demographics stratified on daily average glucose levels over and under 150 mg/dl of 75% time of length of stay (LOS).

n	> 150 mg/dl glucose 47	< 150 mg/dl glucose 59	p value
Gender			
Male	28	40	NS
Female	19	19	
Ethnicity			
African American	2	3	
Caucasian	8	5	
Hispanic	37	50	
other	0	1	
Age at admit	12.1 ± 4.7	7.1 ± 5.1	< 0.05
Inhalation Injury n (%)	32 (68.1)	36 (61.0)	NS
Type of burn			
flame	47 (100.0)	52 (88.1)	
scald	0 (0.0)	3 (5.1)	
other	0 (0.0)	4 (6.8)	
TBSA burn (%)	66.2 ± 19.1	59.4 ± 14.7	
TBSA second (%)	16.0 ± 16.1	17.6 ± 17.1	NS
TBSA third (%)	57.0 ± 26.4	48.3 ± 19.0	NS
Burn to admit (days)	3.1 ± 4.9	3.6 ± 5.9	NS

Abbr.: TBSA = Total Burn Surface Area.

Table 2

Patients' outcome and critical events during the stay in the intensive care unit (ICU). Improved outcome on patients with tight glucose control.

n	> 150 mg/dl glucose 47	< 150 mg/dl glucose 59	p value
Number of OR	5.6 ± 3.4	5.3 ± 4.2	NS
time btw OR (days)	4.7 ± 1.8	5.2 ± 1.5	NS
LOS ICU (days)	43.5 ± 37.7	38.0 ± 25.9	NS
LOS/TBSA	0.7 ± 0.5	0.6 ± 0.3	NS
Non survivors n (%)	13 (27.7)	2 (3.4)	< 0.05
Sepsis n (%)	20 (42.6)	9 (15.3)	< 0.05
Number of Wound Infections	4.1 ± 3.7	2.7 ± 2.4	< 0.05
Duration of mechanical ventilation (days)	10 ± 10	3 ± 2	< 0.05
highest PEEP (mmHg)	11 ± 4	6 ± 2	< 0.05
Worst P/F ratio first 72 h	265 ± 120	259 ± 99	NS

Abbr.: OR=operations, PEEP=positive end expiratory pressure, P/F= ratio of arterial oxygen concentration to the fraction of inspired oxygen.

Table 3

Lung-related complications showing the incidence of pneumonia, incidence of atelectasis and ARDS (adult respiratory distress syndrome).

n	> 150 mg/dl glucose 47	< 150 mg/dl glucose 59	p value
X-ray pneumonia mech. ventilation %	32	21	< 0.05
X-ray pneumonia spont. ventilation %	15	5	< 0.05
total pneumonia %	30	19	< 0.05
X-ray atelectasis on ventilator %	59	61	NS
X-ray atelectasis off ventilator %	47	58	NS
ARDS %	19	3	< 0.05