Published in final edited form as:

Ann Surg. 2013 December ; 258(6): 1119–1129. doi:10.1097/SLA.0b013e3182984d19.

MILD OBESITY IS PROTECTIVE AFTER SEVERE BURN INJURY

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Abstract

Objective—To assess the impact of obesity on morbidity and mortality in severely burned patients.

Background—Despite the increasing number of people with obesity, little is known about the impact of obesity on postburn outcomes.

Methods—A total of 405 patients were prospectively enrolled as part of the multicenter trial Inflammation and the Host Response to Injury Glue Grant with the following inclusion criteria: 0 to 89 years of age, admitted within 96 hours after injury, and more than 20% total body surface area burn requiring at least 1 surgical intervention. Body mass index was used in adult patients to stratify according to World Health Organization definitions: less than 18.5 (underweight), 18.5 to 29.9 (normal weight), 30 to 34.9 (obese I), 35 to 39.9 (obese II), and body mass index more than 40 (obese III). Pediatric patients (2 to 18 years of age) were stratified by using the Centers for Disease Control and Prevention and World Health Organization body mass index-for-age growth charts to obtain a percentile ranking and then grouped as underweight (<5th percentile), normal weight (5th percentile to <95th percentile), and obese (≥95th percentile). The primary outcome was mortality and secondary outcomes were clinical markers of patient recovery, for example, multiorgan function, infections, sepsis, and length of stay.

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Conflict of Interest

The authors declare no conflict of interest.

Results—A total of 273 patients had normal weight, 116 were obese, and 16 were underweight; underweight patients were excluded from the analyses because of insufficient patient numbers. There were no differences in primary and secondary outcomes when normal weight patients were compared with obese patients. Further stratification in pediatric and adult patients showed similar results. However, when adult patients were stratified in obesity categories, log-rank analysis showed improved survival in the obese I group and higher mortality in the obese III group compared with obese I group ($P < 0.05$).

Conclusions—Overall, obesity was not associated with increased morbidity and mortality. Subgroup analysis revealed that patients with mild obesity have the best survival, whereas morbidly obese patients have the highest mortality.

Keywords

burn; obesity; BMI; insulin resistance; inflammation

Introduction

Excessive body weight, or obesity, is associated with myriad diseases as well as with reduced life expectancy.¹ Obesity is commonly defined as a body mass index (BMI, the weight in kilograms divided by the square of the height in meters) greater than 30 kg/m².² The World Health Organization (WHO) uses BMI to determine weight status categories: underweight (BMI <18.5 kg/m²), normal weight (18.5 to 24.9 kg/m²), overweight (25 to 29.9 kg/m²), and obese (>30 kg/m²). As the WHO classification does not apply to children and adolescents, we used the common definition from the Centers for Disease Control and Prevention (CDC), which defines obesity as a BMI >95th percentile.⁴ A recent cohort study including 23 medical centers in 10 different countries and published in the *New England Journal of Medicine* showed that a BMI of 25.3 kg/m² for men and 24.3 kg/m² for women is associated with the lowest risk of death. Furthermore, waist circumference and waist-to-hip ratio is strongly associated with the risk of death.⁵

In the United States, obesity is the second leading cause of preventable deaths after smoking.⁶ Recent increases in adult and childhood obesity have mobilized health professionals to address this serious public health problem. In general, obesity leads to severe health consequences such as coronary heart disease, osteoarthritis, obstructive sleep apnea, social stigmatization, type II diabetes, and certain cancers.⁷ Given the additional associated morbidities including insulin resistance, heightened proinflammatory state, increased triglycerides, and high blood pressure, obesity resembles a metabolic syndrome that is associated with impaired recovery.

A predisposition to impaired recovery would have the potential to endanger obese patients when rapid, unimpeded recovery is essential for survival, such as following trauma or severe burn injury. Therefore, this study was conducted to determine whether obesity is associated with a detrimental outcome in severely burned patients. Four-hundred five patients enrolled in the federally-funded multi-center study Inflammation and the Host Response to Injury Glue Grant were stratified into comparison groups by BMI to determine whether patients with a BMI >30 kg/m² (adults) or in a >95th percentile (children) are prone to greater mortality and morbidity, including infections, sepsis, multi-organ failure (MOF), and prolonged length of stay (LOS), than normal weight patients. We hypothesized that obesity is associated with increased morbidity and mortality after a severe thermal injury.

Materials and methods

Patients

This study was conducted as part of the larger federally funded Inflammation and the Host Response to Injury Glue Grant. The study was approved by the Institutional Review Board of the University of Texas Medical Branch (Galveston, TX), Loyola University Medical College (Chicago, IL), University of Texas Southwestern (Dallas, TX), University of Washington Seattle (Seattle, WA), and Massachusetts General Hospital (Boston, MA). During an 8-year period, 405 patients were prospectively enrolled and met the following inclusion criteria: 0 to 89 years of age, admitted to a participating hospital within 96 hours after injury, and had burns covering more than 20% of total body surface area (TBSA) with at least 1 surgical intervention indicated to provide likely benefit to the patient. After admission, patients were treated according to the standard operating procedures for burn care established by the burn patient-oriented research core.¹² Before participation, written informed consent was obtained from each subject or a family member. Demographics (age, date of burn, date of admission, sex, burn size, and depth of burn) and concomitant injuries (such as inhalation injury, infection, morbidity, and mortality) were prospectively recorded throughout the hospital course.

Body mass index

Body weight was determined daily in patients. The lowest daily weight established for each patient within the first week after the burn injury after diuresis of resuscitation was recorded as the dry weight. BMI was calculated using the standard formula of weight in kilograms divided by the square of the height in meters.¹³ Adult patients (>18 years of age) were stratified into the following groups on the basis of the WHO definitions: less than 18.5 (underweight), 18.5 to 29.9 (normal weight), and 30 or more (obese). Obese adult patients were further stratified by BMI into obese I (BMI 30–34.9), obese II (BMI 35–39.9), and obese III (BMI >40). For pediatric patients (2 to <18 years of age), the BMI was plotted on the Centers for Disease Control and Prevention BMI-for-age growth charts (for either girls or boys) to obtain a percentile ranking. The weight status categories used with children and adolescents were underweight (<5th percentile), normal weight (5th to <95th percentile), and obese (>95th percentile).

Outcomes

The primary outcome was mortality. The incidence, primary cause, and place of death were recorded up to 365 days after burn. Secondary outcomes included incidence of infections, sepsis, MOF, and LOS. We also determined acute and critical care parameters such as blood transfusions and glucose levels. Severity of disease was quantified using the APACHE II score, Baux score, and Denver 2 score. We, furthermore, compared the incidence of nosocomial infections, burn wound infections, pneumonias, positive blood cultures, urinary infections, abdominal compartment syndrome, acute respiratory distress syndrome, cardiac arrests, atrial arrhythmias, and cerebral infarctions.

Mortality was recorded as incidence, primary cause, and place of death up to 365 days after burn.

Disease severity scores—The APACHE II score data presented pertain to the APS (Acute Physiology Score) component of APACHE II, which assesses the first 24 h after injury. This score includes heart rate, respiratory rate, alveolar-arterial oxygen gradient, sodium, potassium, creatinine, white blood cell count, and Glasgow coma scale. The Baux score was calculated as the sum of age and TBSA burned. The Denver 2 is a score of patient status at the first 24 h, calculated as a sum of the following: (i) pulmonary score ranging

from 0 to 3, using PaO₂/FiO₂ cutoffs of 100, 175, and 250; (ii) renal score ranging from 0 to 3, using creatinine cutoffs of 1.8, 2.5, and 5.0 mg/dL; (iii) hepatic score ranging from 0 to 3, using bilirubin cutoffs of 2.0, 4.0, and 8.0 mg/dL; and (iv) cardiac score ranging from 0 to 3 based on number and dosage of inotropes.

Infections—*Nosocomial infections* were recorded when all of the criteria were met as defined in the Inflammation and the Host Response to Injury Glue Grant standard operating protocols.¹² *Burn wound infection* was defined as a burn wound culture resulting in 105 or more colony-forming units (CFUs) per gram of tissue.

Pneumonia was diagnosed when the following criteria were present within a 48-hour period.^{12,18}

- a. New radiographic infiltrate that persists for at least 24 hours.
- b. Temperature more than 38.5°C or less than 35.0°C, WBC count more than 10,000 or less than 3000/mm³.
- c. Bacterial confirmation by at least one of the following:
 - i. Quantitative microbiologic cultures obtained by bronchoalveolar lavage yielding 104 CFU/mL or protected specimen brush yielding more than 103 CFU/mL.
 - ii. Histopathologic examination of lung tissue shows one of a or b.
 - iii. Positive blood culture for bacterial pathogen identified in sputum or respiratory culture.
 - iv. Positive pleural fluid culture with same organism identified in sputum or other respiratory culture.
 - v. Positive sputum gram stain with >3+ of 1 type of pathogenic bacteria. Induced sputum is a positive Gram stain.
 - vi. Heavy or moderate growth of 1 type of pathogenic bacteria on semiquantitative sputum culture.
- d. Abscess formation with intense PMN accumulation in bronchioles and alveoli.
- e. Quantitative culture of lung parenchyma that shows more than 104 CFU/g tissue.

Bloodstream Infections were defined positive when the following conditions were met:

- a. Bacteriologic confirmation: recognized pathogen from one or more blood cultures and the organism cultured was not related to an infection at another site; if a common skin contaminant such as diphtheroids, *Bacillus* species, *Propionibacterium* species, or coagulase-negative staphylococci was present, the organism had to be cultured from at least 2 samples within a 48-hour period.
- b. Clinical criteria (at least one of the following only if the organism identified was a common skin contaminant): Fever more than 38.5°C, WBC count >10,000 or <3000/mm³, hypotension (systolic blood pressure <90 mm Hg), or more than 25% drop in systolic blood pressure.

Urinary Tract Infections were diagnosed when criteria the following were satisfied within a 2-day period:

- a. Clinical criteria (at least one of): Fever more than 38.5°C, WBC count >10,000 or < 3000/mm³, urgency, dysuria, and suprapubic tenderness

- b. Bacterial confirmation: >105 organisms per milliliter of urine.

Abdominal compartment syndrome was defined as an opening of the abdominal cavity for elevated intra-abdominal pressure (>25 cm H₂O) associated with at least one of the following: oliguria (<30 mL/h), diminished cardiac output (<2.5 L/min/m²), and elevated peak/plateau airway pressures (>45 cm H₂O).

Acute respiratory distress syndrome was diagnosed when all of the following criteria were met within a 24-hour period: bilateral infiltrates (acute onset), PaO₂/FiO₂ less than 200 regardless of positive end expiratory pressure, and no evidence of left atrial hypertension (pulmonary capillary wedge pressure <18 if measured) or no evidence of congestive heart failure in the absence of a premature atrial contraction. If a premature atrial contraction is in place, there must be evidence that the pulmonary capillary wedge pressure was more than 18 for at least 12 consecutive hours during the 24-hour assessment block.

Atrial arrhythmia: Abnormal electrical activity was diagnosed by electrocardiogram; events counted in this category included premature atrial contractions, wandering atrial pacemaker, multifocal atrial tachycardia, atrial flutter, and atrial fibrillation.¹⁹

Cardiac arrest was defined as the sudden cessation of cardiac activity (including pulseless electrical activity) after arrival to the emergency department or after admission to the burn unit. *Cerebral infarction* was defined as a new neurologic deficit not present on admission, which was sudden or rapid in onset and lasted longer than 24 hours or until death and confirmed as an infarction by radiography, computed tomography, magnetic resonance imaging, or autopsy.

Statistics

Unpaired Student t-tests and Chi-squared tests were used to compare differences in the variables between groups, where appropriate. Data are expressed as percentages or means ± standard deviation or standard error of the mean (SEM), where appropriate. Log-rank analysis was used for Kaplan-Meier survival curves. Receiver operating characteristic (ROC) analysis was conducted to determine a linear cutoff for the risk of mortality in pediatric patients and in adults. Significance was accepted at a P value of less than 0.05.

Results

The study included 405 burn patients, of whom 273 (67%) had a normal weight and 116 (29%) were obese. Sixteen patients (4%) were underweight; this group was excluded from further analysis due to insufficient sample size. Demographic data are presented in Table 1. Patient demographics such as age, gender distribution, height, percent total TBSA burned, percent third-degree TBSA burned, pre-existing comorbidities, presence of inhalation injury, and burn mechanism (Table 1) were similar in the normal weight and obese groups. LOS, LOS per percent TBSA burned, Baux score, incidence of inhalation injury, Denver 2 score, and Apache score were also similar between the normal weight and obese groups (Table 2).

Obese burn patients received similar amounts of fluids, crystalloids, colloids, and blood products when compared to normal weight burn patients (Table 3). Intensive care unit (ICU) admissions, readmissions, and LOS did not significantly differ between groups. No significant differences were detected between the groups for the number of burn wound infections, days from injury to diagnosis, body region affected, or infectious organism (Table 2). Incidence of nosocomial infections, days from injury to diagnosis of the infection, localization, and organism also did not differ between groups (Fig 1A). Furthermore, no differences were detected between groups for the incidence of abdominal compartment

syndromes, ARDS, cerebral infarction, cardiac arrests, atrial arrhythmia, and amputations (Fig 1B). The mortality rate for the entire population studied was 15%. A Kaplan-Meier survival analysis showed similar survival patterns in normal weight and obese patients, with no significant differences being present between these groups (Fig 1C).

Patients were then further stratified into the following groups: pediatric burn patients (<18 years of age) and adult burn patients (≥ 18 years of age). There were 170 pediatric patients and 235 adults; 8 children and 8 adults were removed from further analyses because of “underweight” categorization. One hundred seventeen pediatric patients were categorized as normal weight (BMI: >5th to 95th percentile) and 45 as obese (BMI: >95th percentile). One hundred fifty-six adults were classified in the normal weight cohort (BMI 18.5–29.9) and 71 patients were obese (BMI ≥ 30). Obese adult patients were further stratified by BMI into obese I (44 patients, BMI 30–34.9), obese II (16 patients, BMI 35–39.9), and obese III (11 patients, BMI >40).

Pediatric burn patients

Demographics and clinical characteristics for pediatric patients are shown in Table 4. Normal weight pediatric patients were significantly older than the obese patients (9 ± 5 years vs 7 ± 5 years, $P < 0.05$). The groups were similar for percent total TBSA burned, percent third-degree TBSA burned, inhalation injury, and burn mechanism. In addition, there were no differences in hospital LOS, body temperature at center arrival, or whether or not patients were ventilated on admission. No statistically significant differences were observed in APACHE II, Baux score and Denver 2 score between normal weight and obese pediatric patients (Table 5). Total amount of colloids infused before admission to the burn unit, number of transfusions, and the quantity of blood transfused during the first 24 and 48 hours after the injury were not significantly different between normal weight and obese pediatric patients (Table 6). Clinical outcomes such as ICU LOS, ICU LOS divided by TBSA, ICU admissions, readmissions, and comorbidities were not significantly different between the pediatric normal weight and obese groups. Furthermore, the number of burn wound infections, nosocomial infections, and the types of infection were similar between the pediatric normal weight and obese patients (Fig. 2A). In addition, hospital morbidity and events were not significantly different between both groups (Fig. 2B). The primary outcome, mortality, was not significantly different between the pediatric normal weight and obese patients (Fig. 2C).

Adult burn patients

Demographics for adult burn patients are shown in Table 7. Percent TBSA, third-degree TBSA, inhalation injury, and burn mechanism were not statistically different between groups. In addition, there was no difference between groups for acute illness parameters including hospital LOS, body temperature, whether or not patients were ventilated on admission, Baux score, APACHE II and Denver 2 score, and comorbidities (Table 8). Similar amounts of fluids, crystalloids, colloids, and blood products were given to the obese and normal weight patients (Table 9). Comparison of infections, ICU LOS, ICU admissions, readmissions, total number of transfusions, total quantity of blood, transfused, comorbidities, and the inpatient medications were not significantly different among the groups (Fig. 3A, B). Mortality for all obese adult patients was the same when compared with all normal weight adult patients (Fig. 3C).

Adults were then stratified into the following cohorts: normal weight and obesity I, II, or III. Demographics were similar between groups except for the stratification variable, BMI (Table 7). In the stratified adult burn patient groups, the number of burn wound infections, infectious organism, nosocomial infections, location of infection, (Fig. 4A), and hospital

events and morbidity were similar in all groups (Fig. 4B). The primary outcome, mortality, in adults was dependent on the obesity grade. In adults, mortality was in obese I (8/44, 12%), normal weight (36/156, 23%), obese II (5/15, 32%), and obese III (7/11, 64%) groups. A Kaplan-Meier survival curve with log-rank analysis showed that the obese I group had the best survival, and that mortality is significantly higher for the obese III group than for the obese I group, $P < 0.05$ (Fig. 4C).

Discussion

The stress reaction following a severe burn requires intact physiological responses to appropriately respond to resultant hypermetabolism and hypercatabolism. This hypermetabolic response is characterized by a hyperdynamic response with concomitant increases in body temperature, oxygen and glucose consumption, CO₂ production, glycogenesis, proteolysis, lipolysis, and futile substrate cycling. A marked acute phase and inflammatory response that continues for at least 36 months post burn and causes loss of lean body mass, loss of bone density, muscle weakness, and poor wound healing is also associated with the hypermetabolic response.^{11,12}

Obesity is one of the fastest growing diseases in modern civilization. Morbidities such as insulin resistance, a prolonged pro-inflammatory state, and hypertension frequently occur in obese patients, which may impact patient recovery after a severe injury. Therefore, in the present study, we asked whether obesity is associated with poor outcomes in burn patients. To our surprise, we found that the outcome for obese burn patients depends on the severity of obesity. Mildly obese patients demonstrated the best outcome, while morbidly obese patients had the worst outcome. Although mild obesity seems, therefore, to be beneficial in terms of outcome postburn, morbid obesity is detrimental and worsens the prognosis of severely thermally injured patients.

Despite the associations of obesity with the development of chronic disease states that lead to early mortality, various studies have described an “obesity paradox” or “reverse epidemiology” in which an improved survival has been observed in obese patients. The obesity paradox was first described by Fleischmann et al²² in 1999 in a study of 1346 hemodialysis patients that demonstrated that the 1-year survival rate was significantly higher in patients with a BMI of more than 27.5 and lower in patients with a BMI of less than 20 than in normal weight patients. Improved survival in obese patients has also been described in cardiovascular pathologies such as heart failure, coronary bypass, and even associated with smaller infarct size after myocardial infarction.^{23–29}

In this multicenter study, we found that overall obesity is not associated with either increased mortality or morbidity in severely burned patients, disproving our initial hypothesis. We found that obese patients have a similar LOS, incidence of infection, sepsis, and complications and similar survival patterns when compared with normal weight patients. Further stratification of the data by obesity grade showed that in adults, the obese I group had the best survival—similar to that of the normal weight group—and that morbidly obese patients had a significantly lower survival. As it was possible that morbidly obese patients were candidates for withdrawal of life-sustaining therapy more frequently than other patients because of preexisting comorbidities or quality-of-life issues, we examined the cause of death for all nonsurviving patients. Evaluation of the cause of death showed that withdrawal of life-sustaining therapy was infrequent in our study, occurring in 7% (3/41) of the normal weight group, in 5% (1/18) of the obese I group, and in none of the patients in the obese II or obese III group. We, therefore, suggest that normal weight and mildly obese patients respond superiorly to critical illness and/or catabolic conditions when compared with morbidly obese patients. Our findings appear in agreement with the large study by

Pischon and colleagues,⁵ in which the authors showed a long-term survival benefit for normal and mildly overweight patients. Furthermore, although our article was under review, a newly released meta-analysis of more than 2.8 million patients with more than 270,000 deaths confirmed that the mildly obese and normal weight patients have reduced all-cause mortality in comparison with patients in obese grade 2 or 3 categories.³⁰ It seems that despite the growing concern to the contrary, normal and mildly obese patients respond appropriately to stress and trauma. However, morbidly obese patients have a higher risk of dying after a severe injury. Despite smaller numbers, our study underscores the necessity for considering morbidly obese patients as an “at risk” group after severe burn injury and for developing specific treatment protocols for reducing risk by attenuating the hypermetabolic and hypercatabolic responses. In the pediatric patients, there were no differences between the obese and normal weight cohorts in terms of clinical outcomes and mortality. Therefore, therapies specific for weight are probably required only for obese adults.

There are limitations of this study that bear discussing in depth. Small patient numbers at the extremes of weight (underweight and morbidly obese subgroups) make it difficult to make an all-inclusive, definitive statement regarding all weights and the risk of postburn mortality. A larger study should be conducted to confirm these results. Additional studies should also include the development of a better classification system for determining “metabolic risk.” BMI is not the ideal way to accomplish this goal, but it is currently the most commonly accepted method for classification despite its shortcomings.³¹ BMI captures the contribution of adiposity but cannot include other factors known to affect fat mass distribution and metabolic rate. The inclusion of age, race, sex, metabolic state, waist circumference, and activity-level measures in an obesity scale would allow evaluation of patients based on metabolic risk. Although investigators are working to identify the most pertinent factors for inclusion in such a scale, one does not currently exist. Similar statements can be made regarding the use of the WHO global child growth standards and growth reference data. These classifications are the most accurate that exist for use in the pediatric population at this time.

Future evaluations of BMI and mortality with greater numbers may be able to include prospective collection of some of these other factors to determine a more comprehensive evaluation based on metabolic risk, obesity, and activity. Our main analyses have shown that mild obesity is protective after severe burn injury in comparison with morbid obesity or being underweight. Mild obesity was also better than normal weight; however, this would have to be confirmed in larger studies with patient numbers exceeding thousands of patients. In this study, we have shown that obesity is not always associated with poor outcome. In contrast, being mildly obese was somewhat protective as shown by the better survival rates when compared with morbidly obese patients and similar survival rates as normal weight patients. There were no differences in morbidity between patient populations. Furthermore, obese children had similar outcomes when compared with normal weight children. We, therefore, suggest that normal and mildly obese patients respond adequately to a severe injury, such as a thermal injury, and are not at greater risk for mortality. Morbidly obese adult patients, however, are at higher risk to die and require tailored care and specialized treatment. These findings could be summarized as follows: “some obesity is good, but too much is bad.” These results imply that many factors related to obesity and metabolism may contribute to the risk of mortality and morbidity in a nonlinear manner.

Rather than create new groups arbitrarily, we chose to use the groupings for underweight, normal weight, and obese grades 1, 2, and 3 that have been well described in the literature. Although we agree that the data should drive the stratification or creation of BMI groups, our data did not suggest the existence of cutoff points despite efforts to identify them. We then conducted an ROC analysis to determine whether there is a linear cut-point for adults

and pediatric patients (data not shown). This analysis was problematic for 2 reasons. First, the power was very weak. Second, this analysis suggested that there was a linear relationship between increasing BMI and increasing mortality for even normal weight individuals. This relationship was not demonstrated through any of our other analyses, nor have we seen an indication of this in the literature. In addition, we found no “tail effect” for increasing obesity, just a steadily increasing risk for mortality as BMI increased. As a result, we have not included the ROC analysis as we do not believe it ourselves. Taking these caveats under consideration, we share the cutoffs that were determined with this suboptimal analysis; in pediatric patients, the 89th percentile was identified as the cutoff whereas a BMI of 28 was identified as the cutoff in adults. We believe that the relationship includes more factors that contribute to making the association of obesity and poor outcome nonlinear. For these reasons, we believe that our log-rank analysis reflects the clinical cutoffs for increased morbidity and mortality in burn patients far better than the ROC analysis.

Of interest was the analysis of the underweight burned patients. Because of insufficient number of patients, we did not include them in the study but believe that the data are intriguing enough to warrant discussion. When we conducted a subanalysis, we found that underweight patients had a significantly higher mortality than obese I and normal weight patients. They also had a higher incidence of infections, sepsis, and multiorgan failure (data not shown). These data indicate that underweight patients may be even at greater risk after a severe injury. This is in agreement with multiple investigations that have examined the impact of low and high BMI in the outcomes of hospitalized and critically ill patients.^{32–34} The recent large meta-analysis confirmed this relationship as well.³⁰ The role of poor nutrition before the burn injury is one aspect of burn care that needs to be examined in a much larger patient population.

CONCLUSIONS

In summary, obesity (BMI >30) was not associated with increased morbidity and mortality after a severe burn injury. Subgroup analysis revealed that mildly obese patients have the best survival rates, whereas morbidly obese patients have the highest postburn mortality. These data indicate that in states of catabolic stress, the existence of energy reserves may in fact confer a survival advantage in patients with BMIs between 30 and 34.9. Confirmatory studies with larger patient numbers should be conducted to develop better predictors of metabolic risk after severe burn injury. However, this study demonstrates the need for the development of therapeutic strategies for use in morbidly obese patients after a severe burn injury.

Acknowledgments

Financial Support: This study was supported by a Large Scale Collaborative Research Grant from the National Institute of General Medical Sciences (U54 GM-62119) awarded to Ronald G. Tompkins and by research grants awarded to David N. Herndon by the National Institute of General Medical Sciences (P50 GM-60338, R01 GM-56687, T32 GM-008256) and Shriners Hospitals for Children (84080, 8760) and to Marc G. Jeschke by the Shriners Hospitals for Children (8660) and the National Institute of General Medical Sciences (R01 GM-087285). CCF is an Institute for Translational Sciences Career Development Scholar supported, in part, by NIH KL2RR029875 and NIH UL1RR029876.

The magnitude of the clinical and proteomic data reported here required the efforts of many individuals at participating institutions. In particular, we wish to acknowledge the supportive research environment created and sustained by the participants in the Glue Grant Program: Henry V. Baker, Ph.D.; Ulysses G.J. Balis, M.D.; Paul E. Bankey, M.D., Ph.D.; Timothy R. Billiar, M.D.; Bernard H. Brownstein, Ph.D.; Steven E. Calvano, Ph.D.; David G. Camp II, Ph.D.; Irshad H. Chaudry, Ph.D.; J. Perren Cobb, M.D.; Joseph Cuschieri, M.D.; Ronald W. Davis, Ph.D.; Asit K. De, Ph.D.; Bradley Freeman, M.D.; Brian G. Harbrecht, M.D.; Douglas L. Hayden, M.A.; Laura Hennessy, R.N.; Jeffrey L. Johnson, M.D.; James A. Lederer, Ph.D.; Stephen F. Lowry, M.D.; Ronald V. Maier, M.D.; John A. Mannick, M.D.; Philip H. Mason, Ph.D.; Grace P. McDonald-Smith, M.Ed.; Carol L. Miller-

Graziano, Ph.D.; Michael N. Mindrinos, Ph.D.; Joseph P. Minei, M.D.; Lyle L. Moldawer, Ph.D.; Ernest E. Moore, M.D.; Avery B. Nathens, M.D., Ph.D., M.P.H.; Grant E. O'Keefe, M.D., M.P.H.; Daniel G. Remick, M.D.; Laurence G. Rahme, Ph.D.; David A. Schoenfeld, Ph.D.; Michael B. Shapiro, M.D.; Richard D. Smith, Ph.D.; John D. Storey, Ph.D.; Robert Tibshirani, Ph.D.; Mehmet Toner, Ph.D.; H. Shaw Warren, M.D.; Michael A. West, M.D., PhD.; Rebbecca P. Wilson, B.A.; and Wenzhong Xiao, Ph.D.

References

- Haslam DW, James WP. Obesity. *Lancet*. 2005; 366:1197–1209. [PubMed: 16198769]
- Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser*. 2000; 894:i–xii. 1–253. [PubMed: 11234459]
- Centers for Disease Control and Prevention. [Accessed April 16, 2009] Healthy weight—it's not a diet, it's a lifestyle!. Available at <http://www.cdc.gov/healthyweight/assessing/bmi/childrensbmi/aboutchildrensbmi.html>
- Ogden CL, Flegal KM, Carroll MD, et al. Prevalence and trends in overweight among US children and adolescents, 1999–2000. *JAMA*. 2002; 288:1728–1732. [PubMed: 12365956]
- Pischon T, Boeing H, Hoffmann K, et al. General and abdominal adiposity and risk of death in Europe. *N Engl J Med*. 2008; 359:2105–2120. [PubMed: 19005195]
- [Accessed April 16, 2006] Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children. Available at <http://www.nice.org.uk/guidance/CG43>
- National Institutes of Health. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. *Obes Res*. 1998; 6(suppl 2):51S–209S. [PubMed: 9813653]
- Bochicchio GV, Joshi M, Bochicchio K, et al. Impact of obesity in the critically ill trauma patient: a prospective study. *J Am Coll Surg*. 2006; 203:533–538. [PubMed: 17000398]
- Christmas AB, Reynolds J, Wilson AK, et al. Morbid obesity impacts mortality in blunt trauma. *Am Surg*. 2007; 73:1122–1125. [PubMed: 18092645]
- Ciesla DJ, Moore EE, Johnson JL, et al. Obesity increases risk of organ failure after severe trauma. *J Am Coll Surg*. 2006; 203:539–545. [PubMed: 17000399]
- Serrano PE, Khuder SA, Fath JJ. Obesity as a risk factor for nosocomial infections in trauma patients. *J Am Coll Surg*. 2010; 211:61–67. [PubMed: 20610250]
- Silver GM, Klein MB, Herndon DN, et al. Standard operating procedures for the clinical management of patients enrolled in a prospective study of inflammation and the host response to thermal injury. *J Burn Care Res*. 2007; 28:222–230. [PubMed: 17351437]
- Eknayan G. Adolphe Quetelet (1796–1874)—the average man and indices of obesity. *Nephrol Dial Transplant*. 2008; 23:47–51. [PubMed: 17890752]
- Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985; 13:818–829. [PubMed: 3928249]
- Osler T, Glance LG, Hosmer DW. Simplified estimates of the probability of death after burn injuries: extending and updating the Baux score. *J Trauma*. 2010; 68:690–697. [PubMed: 20038856]
- Moore FA, Sauaia A, Moore EE, et al. Postinjury multiple organ failure: a bimodal phenomenon. *J Trauma*. 1996; 40:501–510. [PubMed: 8614027]
- Sauaia A, Moore FA, Moore EE, et al. Early risk factors for post injury multiple organ failure. *World J Surg*. 1996; 20:392–400. [PubMed: 8662125]
- Greenhalgh DG, Saffle JR, Holmes JH, et al. American Burn Association consensus conference to define sepsis and infection in burns. *J Burn Care Res*. 2007; 28:776–790. [PubMed: 17925660]
- Marino, PL. *The ICU Book*. 2. Baltimore, MD: Lippincott Williams & Wilkins; 1998.
- Hart DW, Wolf SE, Mlcak R, et al. Persistence of muscle catabolism after severe burn. *Surgery*. 2000; 128:312–319. [PubMed: 10923010]
- Przkora R, Barrow RE, Jeschke MG, et al. Body composition changes with time in pediatric burn patients. *J Trauma*. 2006; 60:968–971. [PubMed: 16688056]
- Fleischmann E, Teal N, Dudley J, et al. Influence of excess weight on mortality and hospital stay in 1346 hemodialysis patients. *Kidney Int*. 1999; 55:1560–1567. [PubMed: 10201023]

23. Lavie CJ, Osman AF, Milani RV, et al. Body composition and prognosis in chronic systolic heart failure: the obesity paradox. *Am J Cardiol.* 2003; 91:891–894. [PubMed: 12667583]
24. Curtis JP, Selter JG, Wang Y, et al. The obesity paradox: body mass index and outcomes in patients with heart failure. *Arch Intern Med.* 2005; 165:55–61. [PubMed: 15642875]
25. Gruberg L, Mercado N, Milo S, et al. Impact of body mass index on the outcome of patients with multivessel disease randomized to either coronary artery bypass grafting or stenting in the ARTS trial: the obesity paradox II? *Am J Cardiol.* 2005; 95:439–444. [PubMed: 15695125]
26. Pingitore A, Di Bella G, Lombardi M, et al. The obesity paradox and myocardial infarct size. *J Cardiovasc Med (Hagerstown).* 2007; 8:713–717. [PubMed: 17700401]
27. Davenport DL, Xenos ES, Hosokawa P, et al. The influence of body mass index obesity status on vascular surgery 30-day morbidity and mortality. *J Vasc Surg.* 2009; 49:140–147. [PubMed: 19028047]
28. Oreopoulos A, Padwal R, Norris CM, et al. Effect of obesity on short- and long-term mortality postcoronary revascularization: a meta-analysis. *Obesity (Silver Spring).* 2008; 16:442–450. [PubMed: 18239657]
29. Oreopoulos A, Padwal R, Kalantar-Zadeh K, et al. Body mass index and mortality in heart failure: a meta-analysis. *Am Heart J.* 2008; 156:13–22. [PubMed: 18585492]
30. Flegal KM, Kit BK, Orpana H, et al. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA.* 2013; 309:71–82. [PubMed: 23280227]
31. Heymsfield SB, Cefalu WT. Does body mass index adequately convey a patient's mortality risk? *JAMA.* 2013; 309:87–88. [PubMed: 23280230]
32. Goulenok C, Monchi M, Chiche JD, et al. Influence of overweight on ICU mortality: a prospective study. *Chest.* 2004; 125:1441–1445. [PubMed: 15078757]
33. Tremblay A, Bandi V. Impact of body mass index on outcomes following critical care. *Chest.* 2003; 123:1202–1207. [PubMed: 12684312]
34. Schmidt DS, Salahudeen AK. Obesity-survival paradox-still a controversy? *Semin Dial.* 2007; 20:486–492. [PubMed: 17991192]

All Patients

Fig 1.
 (A) Incidence of infection, (B) number of hospital events, and Kaplan-Meier survival curves (C) for all burn patients, including pediatric and adult patients. In A and B, data are expressed as mean $\pm$ SEM.

Pediatric Burn Patients

Fig 2.

(A) Incidence of infection, (B) number of hospital events, and Kaplan-Meier survival curves (C) in pediatric burn patients. In A and B, data are expressed as mean $\pm$ SEM.

Adult Burn Patients

Fig 3.

(A) Incidence of infection, (B) number of hospital events, and Kaplan-Meier survival curves (C) in all adult burn patients. In A and B, data are expressed as mean $\pm$ SEM.

Adult Burn Patients Stratified by Obesity I, II, III

Fig 4. (A) Incidence of infection, (B) number of hospital events, and Kaplan-Meier survival curves (C) in adult burn patients divided into Obesity I, Obesity II, and Obesity III groups.

*Significant difference between groups. In A and B, data are expressed as mean $\pm$ SEM.

Table 1

Demographics for all patients (children and adults combined)

Demographic*	Normal Weight (n = 273)	Obese (n = 116)	P value
Age (y)	28 ± 21	28 ± 20	ns
Gender (F/M) [n (%)]	74 (27)/198 (73)	35 (30)/81 (70)	ns
Height (cm)	156 ± 29	152 ± 32	ns
Weight (kg)	58 ± 25	78 ± 39	<0.05
TBSA Burned (%)	49 ± 21	50 ± 20	ns
2nd Degree TBSA (%)	19 ± 18	22 ± 18	ns
3rd Degree TBSA (%)	39 ± 24	39 ± 24	ns
Inhalation Injury [n (%)]	126 (46)	57 (49)	ns
Burn Mechanism			
Flame (%)	82	83	ns
Flash (%)	6	3	ns
Scald (%)	8	9	ns
Other (%)	4	4	ns

TBSA, total body surface area; ns, not significant.

* Data are presented as means ± SD or percentages.

Table 2

Characteristics for all patients (children and adults combined)

Characteristic *	Normal Weight (n = 273)	Obese (n = 116)	P value
Length of stay (days)	42 ± 39	41 ± 37	ns
Length of stay in days/percent TBSA burned	0.88 ± 0.86	0.90 ± 0.79	ns
Denver 2 Score	3 ± 3	3 ± 3	ns
APACHE II Score	18 ± 10	20 ± 10	ns
Baux score	77 ± 23	77 ± 22	ns
Number of burn wound infections	2 ± 1	2 ± 1	ns
Total number of burn operations	7 ± 6	7 ± 5	ns
Number of days on ventilator	14 ± 21	16 ± 19	ns
Total number of events	2 ± 3	2 ± 3	ns
Length of ICU stay (days)	21 ± 24	28 ± 35	ns
Length of ICU stay in days/percent TBSA burned	0.47 ± 0.48	0.61 ± 0.74	ns

TBSA, total body surface area; ns, not significant.

* Data are presented as means ± SD.

Table 3

Resuscitation and transfusion for all patients (children and adults combined)

Resuscitation & Transfusions*	Normal Weight (n = 273)	Obese (n = 116)	P value
Number of transfusions	12 ± 16	11 ± 10	ns
Quantity of blood transfused (ml) 0–24 h	716 ± 655	1277 ± 2042	ns
Quantity of blood transfused (ml) 24–48 h	1962 ± 2456	1789 ± 2028	ns
Worst Base deficit 0–24 h	7 ± 5	8 ± 6	<0.05
Worst Base deficit 24–48 h	4 ± 4	3 ± 4	ns
Total 24-h urine output (ml) 0–24 h	1777 ± 1211	1917 ± 1203	ns
Total 24-h urine output (ml) 24–48 h	1858 ± 1074	1952 ± 963	ns
Glucose (mg/dl) at 8 AM 0–24 h	142 ± 42	148 ± 40	ns
Glucose (mg/dl) at 8 AM 24–48 h	143 ± 40	141 ± 40	ns
Lowest glucose 0–24 h	126 ± 58	123 ± 49	ns
Lowest glucose 24–48 h	113 ± 40	105 ± 30	ns
Highest glucose 0–24 h	187 ± 66	190 ± 68	ns
Highest glucose 24–48 h	189 ± 61	177 ± 58	ns

ns, not significant.

* Data are presented as means ± SD.

Table 4

Demographics for normal and obese pediatric burn patients

Demographic*	Normal Weight (n = 117)	Obese (n = 45)	P value
Age (y)	9 ± 5	7 ± 4	<0.05
Gender (F/M) [n (%)]	41 (35)/76 (65)	9 (20)/36 (80)	ns
Height (cm)	132 ± 29	119 ± 26	<0.05
Weight (kg)	37 ± 21	21 ± 2	ns
TBSA Burned (%)	59 ± 19	62 ± 19	ns
2nd Degree TBSA (%)	22 ± 20	24 ± 24	ns
3rd Degree TBSA (%)	49 ± 25	53 ± 25	ns
Inhalation injury [n (%)]	67 (57)	30 (67)	ns
Burn mechanism			
Flame (%)	80	82	ns
Flash (%)	3	2	ns
Scald (%)	15	13	ns
Other (%)	3	2	ns

TBSA, total body surface area; ns, not significant.

* Data are presented as means ± SD or percentages.

Table 5

Characteristics of normal weight and obese pediatric burn patients

Characteristic *	Normal Weight(n = 117)	Obese(n = 45)	P value
Length of stay (days)	37 ± 43	34 ± 24	ns
Length of stay in days/percent TBSA burned	0.59 ± 0.87	0.52 ± 0.24	ns
Denver 2 Score	1 ± 1	1 ± 1	ns
APACHE II Score	14 ± 9	17 ± 10	ns
Baux score	68 ± 19	69 ± 20	ns
Number of burn wound infections	2 ± 1	2 ± 1	ns
Total number of burn operations	9 ± 7	9 ± 6	ns
Number of days on ventilator	8 ± 15	9 ± 13	ns
Total number of events	2 ± 2	2 ± 1	ns
Length of ICU stay (days)	15 ± 15	20 ± 30	ns
Length of ICU stay in days/percent TBSA burned	0.26 ± 0.25	0.35 ± 0.66	ns

TBSA, total body surface area; ns, not significant.

* Data are presented as means ± SD.

Table 6

Resuscitation and transfusion for normal weight and obese pediatric patients

Resuscitation & Transfusions	Normal Weight (n = 117)	Obese (n = 45)	P value
Number of transfusions	15 ± 15	14 ± 10	ns
Quantity of blood transfused (ml) 0–24 h	655 ± 686	949 ± 1301	ns
Quantity of blood transfused (ml) 24–48 h	1679 ± 2184	2328 ± 2673	ns
Worst Base deficit 0–24 h	−8 ± 5	−10 ± 7	ns
Worst Base deficit 24–48 h	−5 ± 4	−4 ± 4	ns
Total 24-h urine output (ml) 0–24 h	1304 ± 1047	1446 ± 1121	ns
Total 24-h urine output (ml) 24–48 h	1647 ± 1316	1632 ± 925	ns
Glucose (mg/dl) at 8 AM 0–24 h	124 ± 28	147 ± 37	ns
Glucose (mg/dl) at 8 AM 24–48 h	138 ± 42	157 ± 51	ns
Lowest glucose 0–24 h	157 ± 82	152 ± 71	ns
Lowest glucose 24–48 h	122 ± 53	109 ± 26	ns
Highest glucose 0–24 h	194 ± 83	198 ± 83	ns
Highest glucose 24–48 h	196 ± 77	189 ± 88	ns

ns, not significant.

*

Data are presented as means ± SD.

Table 7

Demographic data for adult patients with normal weight and in Obese groups I–III

Demographics*	Normal Weight (n = 156)	All Obese (n = 71)	Obese I (n = 44)	Obese II (n = 16)	Obese III (n = 11)	P value
Age (y)	42 ± 16	41 ± 15	41 ± 14	40 ± 20	39 ± 12	ns
Gender (F/M) [n (%)]	34 (22)/122 (78)	26 (17)/45 (63)	12 (27)/32 (73)	7 (44)/9 (56)	7 (64)/4 (36)	ns
Height (cm)	174 ± 10	172 ± 11	174 ± 10	171 ± 13	166 ± 8	<0.05 [†]
Weight (kg)	75 ± 12	105 ± 18	97 ± 12	110 ± 17	130 ± 16	<0.05 [‡]
TBSA burned (%)	41 ± 20	42 ± 17	41 ± 16	45 ± 21	43 ± 12	ns
2nd Degree TBSA (%)	17 ± 16	21 ± 16	22 ± 15	15 ± 14	23 ± 19	ns
3rd Degree TBSA (%)	31 ± 20	29 ± 18	29 ± 17	34 ± 20	26 ± 19	ns
Inhalation Injury [n (%)]	59 (38)	27 (38)	14 (32)	8 (50)	5 (45)	ns
Burn Mechanism						
Flame (%)	83	83	84	94	64	ns
Flash (%)	9	4	7	0	0	ns
Scald (%)	3	7	5	0	27	ns
Other (%)	5	6	5	6	9	ns

TBSA, total body surface area; ns, not significant.

* Data presented as means ± SD or percentages.

[†] normal weight vs. Obese III.[‡] Normal weight vs. Obese I, II, and III.

Table 8

Characteristics for normal weight and obese pediatric burn patients

Characteristic*	Normal Weight (n = 156)	All Obese (n = 71)	Obese I (n = 44)	Obese II (n = 16)	Obese III (n = 11)	P value
Length of stay (days)	45 ± 36	48 ± 43	50 ± 48	38 ± 21	52 ± 47	ns
Length of stay in days/percent TBSA burned	1.09 ± 0.77	1.13 ± 0.90	1.13 ± 0.95	0.97 ± 0.58	1.34 ± 1.18	ns
Denver 2 Score	2 ± 3	3 ± 3	2 ± 2	3 ± 3	3 ± 4	ns
APACHE II Score	20 ± 9	21 ± 9	20 ± 9	23 ± 10	22 ± 11	ns
Baux score	84 ± 23	83 ± 22	83 ± 21	85 ± 26	80 ± 21	ns
Number of burn wound infections	2 ± 1	2 ± 1	2 ± 1	2 ± 1	2 ± 2	ns
Total number of burn operations	5 ± 4	5 ± 4	5 ± 5	5 ± 4	5 ± 4	ns
Number of days on ventilator	18 ± 24	20 ± 22	17 ± 17	24 ± 22	25 ± 35	ns
Total number of events	2 ± 3	2 ± 2	3 ± 3	3 ± 3	3 ± 3	ns
Length of ICU stay (days)	32 ± 34	37 ± 42	38 ± 48	33 ± 21	40 ± 45	ns
Length of ICU stay in days/percent TBSA burned	1.98 ± 0.62	0.77 ± 0.74	0.78 ± 0.79	0.74 ± 0.79	0.80 ± 0.85	ns

TBSA, total body surface area; ns, not significant.

* Data are presented as means ± SD.

Table 9

Resuscitation and transfusion data for adult patients with normal weight and in Obese groups I–III

Resuscitation & Transfusions*	Normal Weight (n = 156)	All Obese (n = 71)	Obese I (n = 44)	Obese II (n = 16)	Obese III (n = 11)	P value
Number of transfusions	9 ± 16	9 ± 10	8 ± 10	10 ± 10	9 ± 11	ns
Quantity of blood transfused (ml) 24–48 h	2313 ± 2772	1251 ± 892	893 ± 657	1853 ± 703	1776 ± 1691	<0.05 [†]
Worst Base deficit 0–24 h	-6 ± 5	-7 ± 6	-7 ± 5	-7 ± 5	-11 ± 9	ns
Worst Base deficit 24–48 h	-3 ± 3	-3 ± 4	-3 ± 3	-3 ± 3	-4 ± 4	ns
Total 24-h urine output (ml) 0–24 h	1897 ± 1223	2028 ± 1202	1944 ± 1322	1944 ± 1322	2009 ± 1036	ns
Total 24-h urine output (ml) 24–48 h	1932 ± 970	2062 ± 958	1912 ± 870	1912 ± 870	2339 ± 1310	ns
Glucose (mg/dl) at 8 AM 0–24 h	143 ± 43	148 ± 41	144 ± 31	144 ± 31	146 ± 35	ns
Glucose (mg/dl) at 8 AM 24–48 h	144 ± 40	137 ± 37	139 ± 40	139 ± 40	150 ± 33	ns
Lowest glucose 0–24 h	111 ± 30	110 ± 24	113 ± 25	113 ± 25	104 ± 25	ns
Lowest glucose 24–48 h	108 ± 29	104 ± 32	108 ± 32	108 ± 32	103 ± 34	ns
Highest glucose 0–24 h	184 ± 56	186 ± 60	189 ± 53	189 ± 53	165 ± 44	ns
Highest glucose 24–48 h	185 ± 49	171 ± 40	168 ± 30	168 ± 30	175 ± 47	<0.05 [‡]

* Data are presented as means ± SD.

[†] normal weight vs. Obese I.[‡] normal weight vs. all obese.