The effect of obesity on adverse outcomes and metabolism in pediatric burn patients

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Abstract

Hypothesis—Obesity influences metabolism and increases the incidence of clinical complications and worsens outcomes in pediatric burn patients.

Design—Retrospective, single-center study.

Subjects—Five hundred ninety-two severely burned pediatric patients who had burns covering more than 30% of the total body surface area and who were treated between 2001 and 2008 were enrolled in this study. Patients were divided into 85th percentile (n = 277) and normal (n = 315) weight groups based on body mass index percentiles.

Results—Patients stratified below (normal) and 85th percentile had similar age, gender distribution, and total burn size. No significant differences were detected in the incidence of sepsis (11% for obese vs. 10% for normal), the incidence of multiple organ failure (21% for obese and 16% for normal), or mortality (11% for obese vs. 8% for normal). Compared to the normal group, the 85th percentile group had low levels of constitutive proteins (α2macroglobulin and Apolipoprotein A-1) ($p < 0.05$ for both) as well as high levels of triglycerides and the acute-phase protein, C-reactive protein ($p < 0.05$ for both) up to 60 days after injury. Patients 85th percentile showed a significant higher loss of bone mineral density and lipolysis compared to normal individuals. Stepwise logistic regression analysis revealed that body mass index had a positive predictive value towards the maximum DENVER2 score, an index of organ failure ($p < 0.001$).

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Conclusions—BMI   85th percentile altered the post-burn acute phase and catabolic response but did not increase the incidence of sepsis, multiple organ failure, or mortality in pediatric burn patients. Our results suggest that impaired metabolism and an altered inflammatory response occurs already in patients starting at the 85th percentile BMI.

Keywords

childhood obesity; pediatrics; burn injury; overweight; hyper metabolism; catabolism

INTRODUCTION

One of the earliest investigations of the morphologic and functional changes in the body that are caused by obesity was published in 1880 [1]. The increasing prevalence of obesity in our modern society has led to an intense focus on the impact of obesity on all aspects of human health. Physiologic derangements caused by obesity and a range of multiple organ dysfunctions have been extensively investigated over the decades. Recent studies have examined weight as an important predictor of morbidity and mortality during the hospital stay.[2-4] Obesity is a well-established and important risk factor in the critically ill patient, especially after major surgery and severe trauma [3, 5-7]. Management of the morbidly obese patient and their often complicated anatomy requires major technical skills, not only in surgical treatments to promote wound healing [3], but also in critical care management [5, 7, 8]. Recent studies have revealed that obesity leads to a profound and persistent pro-inflammatory state [9, 10]. This is caused by an impaired immune system and a metabolic response that differs from that seen in the healthy patient population. Thermal injury has been shown to lead to a severe hypermetabolic response and an excessive inflammatory response, inducing multiple organ failure (MOF) and global catabolism [11, 12]. The role of obesity in this patient population is currently discussed controversially. It is often hypothesized that obese patients might benefit from the caloric reserves during the catabolic state followed burn injury. Up-to-date there is very little data regarding the impact of the BMI on clinical outcomes in this burn specific topic. The aim of this study was to determine the effect of obesity on the post-burn hypermetabolic, hypercatabolic response in pediatric patients as well as to identify the main organ systems affected by obesity after burn injury, and to identify major clinical challenges.

MATERIALS AND METHODS

Patients

Five hundred and ninety-two pediatric patients who had burns covering over 30% of the total body surface area (TBSA) and who were admitted to our burn center between 2001 and 2008 were included in this retrospective study. Patients were assigned to groups according to their body mass index (BMI), calculated according to the equation BMI = weight (kg) / height^2 (m^2) using their weights and heights at admit. In patients under 20 years old, BMI percentile was determined according to published charts for age and gender[13]. Children were stratified in the following patient cohorts: BMI <85th%tile (Normal/N), 85th%tile to <90th%tile (Overweight/OW), 90th%tile to <95th%tile (Obese/OBE), 95th%tile (morbidly obese/MOBE) for survival analysis. A second assignment was performed according the

results of ROC analysis on mortality for clinical outcomes and clinically relevant biochemical markers.

If indicated, patients were resuscitated according to the Galveston formula, with 5,000 cc/m^2 TBSA burned + 2,000 cc/m^2 TBSA lactated Ringer's solution being given in increments over the first 24 hrs. Within 48 hrs of admission, all patients underwent total burn wound excision, and the wounds were covered with autograft. Any remaining open areas were covered with homograft. After the first operative procedure, patients returned to the operating room when their skin graft donor sites were healed for further grafting as needed. This procedure was repeated until all open wound areas were covered with autologous skin.

All patients received the same nutritional treatment according to a standardized protocol. The intake was calculated as 1,500 kcal/m^2 body surface + 1,500 kcal/m^2 area burn, as previously published [14]. Patients received enteral nutrition via a duodenal (Dobhoff) or nasogastric tube. Parenteral nutrition was only given in rare instances if the patient could not tolerate tube feeds.

Patient demographics (age, date of burn, date of admission, sex, burn size, and burn depth), concomitant injuries such as inhalation injury, sepsis, morbidity, and mortality were recorded. Sepsis was defined as a positive blood culture or pathologic tissue specimen during hospitalization or at autopsy, in combination with at least three of the following: leucocytosis or leucopenia (>12,000 or <4,000, respectively), hyperthermia or hypothermia (>38.5°C or <36.5°C, respectively), tachycardia (>150 bpm in children), refractory hypotension (systolic BP <90 mmHg), thrombocytopenia (platelets <50,000/mm^3), hyperglycemia (serum glucose >240 mg/dl), and enteral feeding intolerance (residuals >200 cc/hr or diarrhea > 1 L/day), as described previously[15]. Because patients return to the operating room as soon as the donor sites heal, the time between operations served as an estimate of wound healing and re-epithelization.

Multiple organ failure

Organ failure was calculated according the DENVER2 score[16]. Organ failure defined as a Denver2 Score exceeding 3. MOF was defined as two different organ failures on two consecutive days.

Body composition (DEXA Scans)

Height and body weight were determined at 5 days after admission and at discharge. Total lean body mass, body fat, bone mineral density, and bone mineral content were measured by dual energy x-ray absorptiometry (DEXA). A QDR-4500W DEXA scanner (Hologic Inc, Waltham, MA) was used to determine body composition, as previously described [12].

Indirect calorimetry

As part of our routine clinical practice, all patients underwent resting energy expenditure (REE) measurements within one week of hospital admission and weekly thereafter during their acute hospitalization. All REE measurements were performed between midnight and 5 a.m. while the patients were asleep and receiving continuous feeding. REE was measured

using a Sensor-Medics Vmax 29 metabolic cart (Yorba Linda, CA) as previously described [14]. REE was calculated from the oxygen consumption and carbon dioxide production using equations described by Weir.[17]. Measured values were compared to predicted norms based upon the Harris-Benedict equation and to BMI [14]. For statistical comparison, energy expenditure was expressed as both absolute REE and the percentage of the basal metabolic rate predicted by the Harris-Benedict equation.

Analysis of cytokines and other proteins

Blood was collected from burn patients at admission, pre-operatively, and for up to 60 days during their ICU stay. Blood was drawn in a serum-separator collection tube and centrifuged for 10 min at 1,320 rpm. The resulting serum was collected and stored at −70°C until analysis for cytokines and proteins.

Serum acute-phase proteins were determined using high-performance liquid chromatography, nephelometry (BNII, Plasma Protein Analyzer Dade Behring, MD), and ELISA. The Bio-Plex Human Cytokine 17-Plex panel was used with the Bio-Plex Suspension Array System (Bio-Rad, Hercules, CA) to profile expression of the following 17 inflammatory mediators: interleukins (IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p70, IL-13, IL-17, granulocyte colony stimulating factor, granulocyte macrophage colony stimulating factor, interferon-gamma, monocyte chemoattractant protein-1, macrophage inflammatory protein-1 beta, and tumor necrosis factor (TNF). The assay was performed according to the manufacturer's instructions. Briefly, serum samples were thawed, centrifuged at 4,500 rpm for 3 min at 4°C, and incubated for 30 min with microbeads labeled with specific antibodies to the aforementioned cytokines. Following a wash step, the beads were incubated with the detection antibody cocktail, which consisted of antibodies specific to each cytokine. After another wash step, the beads were incubated with streptavidin-phycoerythrin for 10 min and washed. The concentrations of each cytokine were then determined using an array reader [18].

Ethics and statistics

This 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 legal guardian signed a written informed consent form. For the cut-off analysis, Receiver Operating Characteristic (ROC) analysis was used. Student's *t*-tests, and Chi-square test were used where appropriate. Data are expressed as the mean ± SD or SEM. Values of *p* less than 0.05 were accepted as significant. Statistical analysis was performed using Microsoft Excel® and Systat Software Sigmastat® version 3·5 and Sigmaplot®, Systat Software Inc. (San Jose, CA, USA).

RESULTS

Mortality and Cut Off Analysis

Normal, overweight, obese, and morbidly obese patients were similar in their demographics and injury characteristics (N: 56 ± 17, OW: 53 ± 15, OBE: 58 ± 19, MOBE: 57 ± 18 % burn TBSA). Only morbidly obese patients were significantly younger (N: 9 ± 4, OW: 9 ± 4,

OBE: 10 ± 5, MOBE: 8 ± 5 years) than normal weight patients and were admitted significantly earlier compared to normal and overweight patients (N: 5.0 ± 5.2, OW: 2.7 ± 2.9, OBE: 3.8 ± 4.6, MOBE: 2.6 ± 2.8 days).

Mortality did not differ significantly among the groups (N: 25 (7.9%), OW: 5 (10.0%), OBE: 9 (10.8%), MOBE: 17 (11.8%). Long term mortality as well as mortality shown for the first 100 days post burn (Fig. 1a) signalized impaired outcomes for patients 85th percentile (85.4th percentile) but did not reach significance (p=0.442). ROC analysis (Fig. 1b) also supported this finding and suggested a cut off around the 85th (A= 0.5964, p=0.0175) percentile. Low AUC indicate for other major contributing factors for mortality exists and does not deliver a sensitive and specific cut off point.

Demographics

The 85th percentile and normal group were similar in age, gender, ethnicity, burn mechanism, length of hospital stay, and incidence of inhalation injury (Table 1). As expected, the 85th percentile patients were heavier than normal weight patients ($p < 0.05$). Organ-specific stratification of MOF observed over time revealed no remarkable differences in individual organ function between groups (Fig.2a). However, the 85th percentile group had a significantly higher maximum MOF scores (p<0.05) over time (DENVER2), and increasing BMI correlated positively (p<0.001) with the incidence of MOF (Fig. 2b). Patients 85th percentile had an increased number of operations ($p < 0.05$). Normalization of the length of hospital stay according burn size did not uncover any differences between 85th percentile and normal weight patients. No significant differences were detected between the two groups in the number of infections, the incidence of sepsis, MOF, or mortality (Table 1, Fig. 2).

Cytokines, constitutive proteins, and acute-phase proteins

Cytokine levels did not differ between groups during the observed period (TNF and IL-6 are representative of cytokine responses in obese and normal patients, Fig. 3 a,b). In contrast, levels of insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) varied between groups (Fig. 3 c,d, $p < 0.05$). Of the constitutive and acute-phase proteins measured, Apolipoprotein A1 (ApoA1), Apolipoprotein B (ApoB), alpha-protein Macroglobulin (A2 Macro), and C-reactive protein (CRP) are displayed (Fig. 4 a-f). ApoA1, ApoB, and A2 Macro were lower in the 85th percentile group than in the normal group ($p < 0.05$). Conversely, CRP levels were higher in the 85th percentile group than in the normal group ($p < 0.05$). The 85th percentile group also had higher levels of triglycerides ($p < 0.05$) and discrete higher alkaline phosphatase (ALP) levels, an indicator of hepatic function. Measurement of renal function, as defined by the DENVER2 score, did not reveal any significant differences between the groups.

Body composition

A significant loss in bone mineral density occurred in the 85th percentile group from admission to discharge, whereas normal weight patients showed no major change during this time (Fig. 5a). Both populations gained whole body fat during the hospital stay, with a

significant relative increase occurring in the normal weight group. The loss of lean body mass was nearly equal in both groups.

Indirect calorimetry

REE was significantly increased in both groups from admission to discharge ($p < 0.05$). However, no significant difference was detected between the groups (Fig. 5b).

DISCUSSION

Obesity is a well-established risk factor for poor outcomes in adult patient populations [19], and several studies of obese patients undergoing major elective and non-elective operations have identified an increase in morbidity and mortality.[2, 20, 21] Obesity is associated with chronic cardiac diseases, and dysfunctional metabolism.[22] It is also known to induce a whole-body pro-inflammatory state and impair immune responses, triggering a hyper inflammatory response and diminishing defenses against microorganisms. [5, 23, 24] Obesity-related changes in physiology and anatomy present a surgical challenge, increasing complication rates and extending operation times.[25] Despite the serious nature of obesity-related sequelae, morbidity associated with obesity in critically ill pediatric patients has been largely ignored. Even fewer studies have been conducted in the pediatric burn patient population. The increasing prevalence of obesity in children is leading to a new focus on this disease in the pediatric patient population. In most cases, childhood obesity is not associated with a high incidence of preexisting chronic co-morbidities such as diabetes mellitus, cardiac diseases, and other impaired systemic functions. However, whether obesity increases risks to the pediatric patient population after trauma or burn trauma has not been fully evaluated. Given all of the negative physiological effects of obesity, we conjectured that obesity would worsen the outcome of pediatric patients following burn injury.

We investigated the effect of body weight on acute hospitalization after severe burn injury in the pediatric population. The hypermetabolic response is one of the most severe complications after thermal injury and leads to an increased catabolic state, with whole-body protein breakdown and loss of body mass. Our group and others have found that severe burn injuries, much like other critical illnesses, lead to a profound catabolic state, decreased immune function, impaired wound healing, and increased mortality [26-28]. At the time of admission, the two patient groups were highly similar. The finding that the 85th percentile group had a significantly higher number of operating room visits may indicate that increased body weight plays a role in delaying the recovery of these patients following severe injury. Since the patients had a similar TBSA burned, we might have expected that the clinical progression of recovery would be almost identical. The incidence of MOF was not significantly different in overweight pediatric patients stratified according the WHO guidelines, despite the fact that logistic regression indicated that increasing BMI was predictive of MOF. This may be indicative that pediatric patients with a higher BMI may have a significant impaired organ function. However regarding mortality no differences were found in this stratification. The results of the cut off analysis suggest that increasing BMI does not affect the mortality in pediatric burn patients. The not significant differences

among the groups signalize that other co factors such as preexisting conditions might have a more direct influence on survival as it can be seen in adult patient populations[29].

Overweight pediatric burn patients experienced a significantly greater loss in bone mineral density than normal weight children during the study period. This underscores the fact that size does not denote pathophysiologic gains or losses after burn injury. Change in fat composition in these patients was also significantly different. However our results indicate that stored caloric reserves do not decrease resting energy expenditure nor prevent significantly from the loss of lean body mass. Further long-term studies are needed to determine whether obese patients recover lost bone mineral density or fat and how an adjusted treatment regimen could prevent this loss.

Overall, both patient groups had significantly greater cytokine levels than non-burned patients. However, our finding that cytokine levels did not differ between obese and normal children was unexpected. Researchers have previously found that immune responses differ between obese adult patients and normal adults. However we were not able to detect significant differences in our pediatric burn population. These differing results could be attributable to the fact that cytokines are part of the adaptive immune system and differences in their response might be caused by BMI with increasing age[30]. Alternatively, the effects of burn injury on the inflammatory system may far outweigh the contribution of obesity in altering inflammation. Greater levels of IGF-1 and IGFBP-3 in the normal weight population, even at admit, may be indicative of derangements in the hormonal or hepatic responses of obese pediatric patients, which might also affect several metabolic pathways.

The finding that overweight pediatric patients had higher CRP and triglyceride levels combined with BMD and fat loss than normal weight patients is consistent with the increased pro-inflammatory, catabolic state of obese patients [31, 32]. Higher ApoB, ApoA1, and A2-Macro levels in the normal group may point to altered protein metabolism and hepatic function in overweight patients.

Although the hepatic component of the DENVER 2 score demonstrated that liver function was similar in both normal and obese patients, the results of our hormonal and proteomic profiling suggest that this is not the full story. Blunted alterations in IGF-1 or IFGBP-3 production and greater CRP levels in obese patients may indicate that liver function in obese pediatric burn patients is, in fact, different than that in normal weight patients.

CONCLUSIONS

The finding that increasing BMI did not increase mortality significantly in this large group of pediatric burn patients does not imply that obesity also has a similar lack of effect on morbidity. Indeed, the BMI was predictive of MOF, a significant cause of death after severe burn injury, indicating that a relationship exists between body weight and MOF in pediatric burn patients. Future studies stratifying the obese population into smaller subcategories might uncover the effects of obesity on inflammation and different organ function. Clinically important overweight patients showed a greater loss in bone mineral content and fat indicating for an altered catabolic response. Our results indicate that changes in hormonal

and metabolic functions occur already in patients with a BMI below the 90th percentile BMI in overweight patients. Additional research will also be necessary to investigate the genomic and proteomic pathways that leads to MOF as well as the relationship between BMI and organ function following severe trauma.

ACKNOWLEDGMENTS

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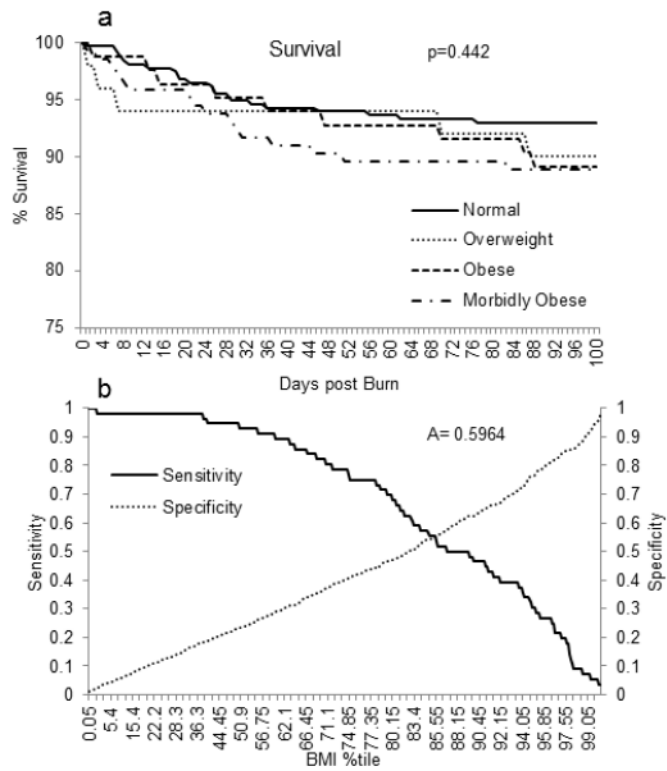
Figure 1. Cut off and survival analysis of normal weight, overweight, obese, and morbidly obese patients

Mortality in all patient populations was similar during the acute phase and for the first 100 days. ROC analysis suggested impaired survival beyond the 85th percentile BMI at a non sensitive and specific level.
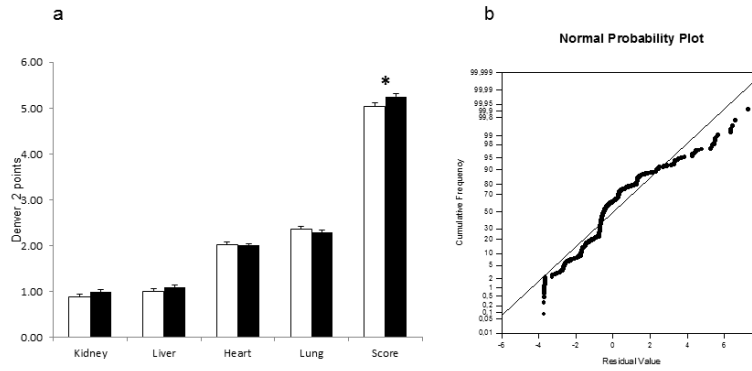
Figure 2. Obesity is associated with multiple organ failure, as seen by DENVER2 scores
Detailed analysis of organ-specific dysfunction, showing that a higher total DENVER2 score in obese patients is caused by liver and kidney dysfunction (a). The normal probability plot, showing that total DENVER2 scores increase with increasing body mass indices in the whole study population ($p<0.001$) (b).
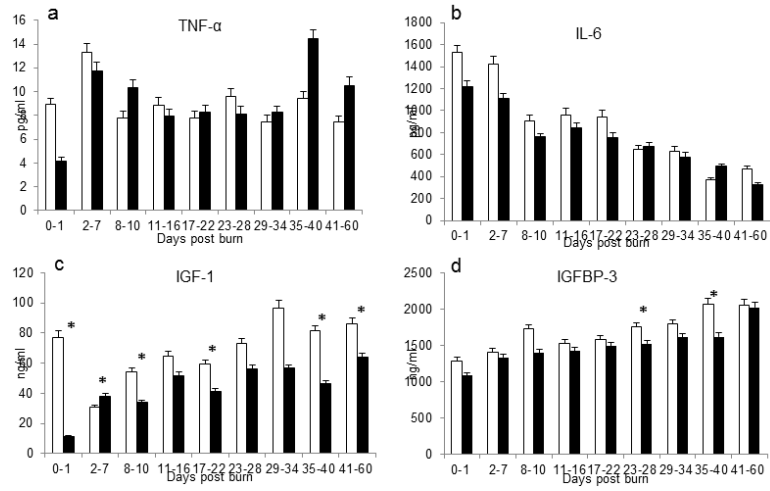
Figure 3. Comparison of cytokine, IGF-1, and IGFBP-3 levels in obese and normal weight patients

Cytokine responses, exemplified by TNF-a and IL-6, were comparable between both groups, while IGF-1 and IGFBP-3 expression was higher in the normal weight group.
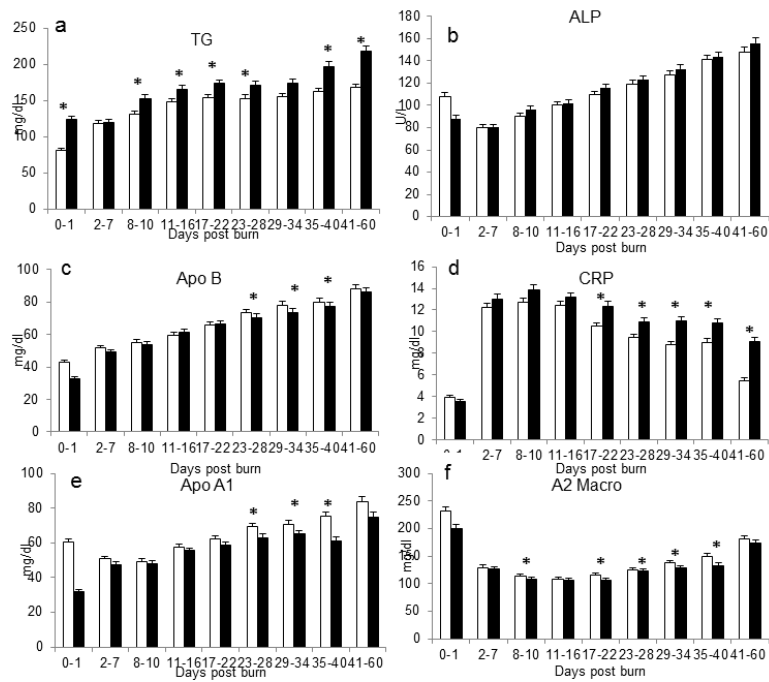
Figure 4. Comparison of hepatic protein, C-reactive protein, triglyceride, and alanine aminotransferase levels in obese and normal weight patients

Normal patients showed a significant better synthesis rate of hepatic proteins and elevated systemic ALP levels. Patients ≥ 85th percentile exhibited a greater response of the acute-phase protein CRP and of triglycerides.
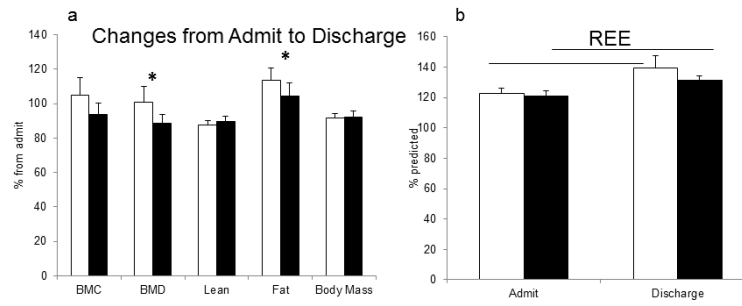
Figure 5.
Effect of obesity on body composition (a) and resting energy expenditure (b).

Table 1

Patient demographics

First column show Both patient cohorts stratified according the calculated cut off of the 85th percentile were similar in demographics and injury characteristics.

	All	< 85th percentile	85th percentile	p value
n	592	315	277	
BMI %ile	72 ± 29	52 ± 27	94 ± 4.4	< 0.05
BMI	20 ± 5	17 ± 3	22 ± 4.8	< 0.05
Gender				
Male n	402	216	186	
Female n	190	99	91	
Ethnicity				
African American n	37	20	17	
Caucasian n	86	41	45	
Hispanic n	455	243	212	
Other n	14	11	3	
Age at Admit (years)	8.9 ± 4.8	9.2 ± 0.3	8.5 ± 0.3	NS
Inhalation Injury n (%)	178 (30.1)	90 (28.6)	88 (31.8)	NS
Type of burn				
Flame n (%)	445 (75.2)	238 (75.6)	207 (74.7)	
Scald n (%)	97 (16.4)	46 (14.6)	51 (18.4)	
Other n (%)	50 (8.4)	31 (9.8)	19 (6.9)	
% TBSA burn	56.0 ± 17.5	55.8 ± 1.0	56.2 ± 1.1	NS
% TBSA third	38.8 ± 26.5	37.8 ± 1.5	40.1 ± 1.6	NS
Burn to admit (days)	4.1 ± 4.6	5.0 ± 0.3	3.0 ± 0.2	<0.05

Table 2

Clinical outcomes

Patients ≥85th percentile and normal weight patients showed a similar clinical complication rate. Higher maximum DENVER2 scores reflected more severe organ failure related complications in the ≥85th percentile group.

	< 85th percentile	85th percentile	p value
OR n	3.7 ± 0.2	4.3 ± 0.2	<0.05
LOS ICU (days)	27.4 ± 1.4	29.0 ± 1.5	NS
LOS/TBSA	0.5 ± 0.1	0.5 ± 0.1	NS
Died n (%)	25 (7.9)	31 (11.2)	NS
Max DENVER2	3.3 ± 0.1	3.6 ± 0.1	<0.05
MOF n (%)	50 (15.9)	59 (21.3)	NS
Sepsis n (%)	31 (9.8)	31 (11.2)	NS
Infections n	2.3 ± 0.2	2.5 ± 0.2	NS