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# Obese Patients Show a Depressed Cytokine Profile Following Severe Blunt Injury

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## Abstract

**Objective—**We hypothesized that severely injured obese patients would display increased concentrations of pro-inflammatory cytokines when compared to patients of normal body mass index (BMI), and that this would be associated with multiple organ failure (MOF).

**Design—**Retrospective review of prospectively collected data in the “Inflammation and the Host Response to Injury” trauma-related database.

**Setting—**Data was collected prospectively from United States Level I trauma centers

**Patients—**Severely injured adult blunt trauma patients

**Measurements—**Cytokine concentrations obtained within 12 hrs of injury and on days one and four were compared between subjects on the basis of BMI (Normal, 18.5-24.9 kg/m$^2$ and Obese, ≥ 30 kg/m$^2$). Demographic measures, injury severity, cytokine concentrations, and outcome measures were compared between groups.

**Main Results—**74 adult blunt trauma victims were evaluated. Relative to patients of normal BMI (n=34), obese patients (n=40) demonstrated an overall depressed cytokine response to severe

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injury, with significantly lower concentrations of several cytokines. Obese patients showed greater incidences of nosocomial infection (60 vs. 45%, NS) and MOF (63% vs. 44%, NS) and a later onset of maximum MOF score (5 days vs. 3, $p<0.04$) when compared to those of normal BMI.

**Conclusions—**Despite prior reports suggesting a pro-inflammatory cytokine profile in obese individuals, obese patients sustaining severe injury show a depressed early cytokine response when compared to patients of normal BMI. This may confer increased susceptibility to nosocomial infection and later MOF. Further study of immune dysfunction in the post-injury obese patient should assess the possibility of early immune suppression.

### Keywords

Obesity; trauma; inflammation; cytokines

## Introduction

Obesity is a significant public health problem, and the impact of caring for increasing numbers of obese individuals is being felt worldwide and across medical disciplines. Both animal and human studies have demonstrated that obesity is associated with adverse health consequences, including susceptibility to a diverse group of diseases affecting the cardiovascular, pulmonary, renal, and endocrine systems (1-7). A growing body of literature has been devoted to examination of the pathophysiologic mechanisms that link obesity to these maladies, with a general consensus that chronic inflammation provides the connection (8-17).

Within the fields of trauma and surgical critical care, increasing attention is being paid to the impact of obesity on patients suffering severe injury. Many investigators have demonstrated an association between obesity and poor outcomes following injury, with the heavier patient showing increased rates of specific infectious and non-infectious complications, multiple organ failure (MOF), and death (18-29). We have previously hypothesized that the baseline pro-inflammatory state of the obese patient would at least partially explain differences in outcome between patients of normal and increased body mass index (BMI) (30, 31). To explore this, we utilized the “Inflammation and the Host Response to Injury” (Glue Grant) Trauma-Related Database (TRDB) to evaluate the possibility of a differential inflammatory response to severe blunt trauma by both static and dynamic measurements of leukocyte genomic expression in the 28 days following injury (30). This study showed no differences in initial inflammatory response (within the first 12 hours following injury), but did suggest differences in genomic expression over time that may be associated with the development of post-injury complications in morbidly obese patients.

An additional means of measuring system-wide inflammation both at baseline and injury is quantification of serum cytokine levels. Elevated levels of IL-6 and IL-10 have been shown to be predictive of poor outcomes following trauma, and in particular, are associated with post-injury MOF (32, 33). Since our previous publications, the Glue Grant investigators have completed evaluation of cytokine profiles on the study's sampling patient cohort, providing another opportunity to evaluate the role of inflammation as a possible causative mechanism in the adverse outcomes of the obese trauma patient. As obese individuals have

been shown to have a pro-inflammatory cytokine profile at baseline and an increased predisposition to develop MOF following trauma, we hypothesized that injured obese patients would display increased concentrations of pro-inflammatory cytokines when compared to patients of normal BMI, and that this would correlate with MOF.

## Materials and Methods

Prior to initiation of this project, approval was obtained from the University of Florida Institutional Review Board to analyze de-identified data obtained from the "Inflammation and the Host Response to Injury" Trauma-Related Database (TRDB).

We performed a retrospective review of clinical data and serum cytokine levels present in the "Inflammation and the Host Response to Injury" TRDB for injured and control patients. Inclusion and exclusion criteria for injured patients enrolled in the study are as previously outlined (30): (1) patients with ages between 16 and 55 with blunt trauma; (2) an abbreviated injury scale (AIS) severity score greater than 2 outside the head region; (3) emergency department arrival less than six hours from the time of injury; (4) base deficit greater than 6 mEq or systolic blood pressure less than 90 mmHg in the prehospital phase of care, or within 60 minutes of arrival; (5) blood transfusion within 12 hours of injury; and (6) intact cervical spinal cord. Patients were excluded if they had (1) a prehospital Glasgow Coma Scale score of less than 8 or died within the first 48 hours of hospitalization; or (2) lacked the information needed to calculate BMI, or if their BMI was less than 18.5. For our specific analysis, only patients who had samples drawn at all time points (days zero (within 12 hours of injury), one (24 hours following injury), and four (96 hours following injury)), were included.

Injured patients were stratified into two BMI categories: normal (BMI 18.5-24.9); and obese (BMI ≥30). Patients with BMI between 25 and 29.9 (NIH/WHO "Overweight") were not considered in this analysis. For comparative purposes, continuous data in the two groups were log transformed and Two Way ANOVA for repeated measures was utilized to compare groups with respect to BMI class and time. Results were then back-transformed for the purpose of presentation in the manuscript and figures. Continuous variables were otherwise compared utilizing student's t-test. Chi-Square or Fisher Exact Tests were used to compare proportional variables as indicated. Pair-wise comparison tests were utilized where appropriate. Results were considered significant when p-value was less than 0.05. Statistics were calculated using SigmaStat© 2.03 (SPSS Inc., Chicago, IL).

## Results

### Study Population

125 patients were identified in the database with serum cytokine measurements. 74 patients met the inclusion and exclusion criteria for this study. Demographic and general clinical information for the entire study population can be seen in **Table 1**.

### Comparison of Patients of Normal BMI with Obese Patients

We compared patients of normal BMI to those designated as obese (**Table 2**). The obese patient cohort was noted to have developed MOF at a greater rate (63 vs. 44%, NS) and two days later (Day 5 vs. Day 3, p=0.04) than patients with normal BMI. Additionally, their nosocomial infection rate was greater (60% vs. 45%, NS). Importantly, obese patients showed an overall depressed cytokine response to injury when compared to normal patients (**Table 3, Supplemental Figures 1-9**).

## Discussion

Post-injury immune dysfunction is a well-documented phenomenon, although the timing, mechanisms, and treatment of this dysfunction and the prevention of its consequences have yet to be fully elucidated (35). What is clear is that there is ample evidence of dysfunction in multiple cell populations noted by a number of immune markers, and the contribution of each of these likely contributes to the clinical effect.

Previous authors have noted differences in multiple cytokines and a relationship with post-injury MOF. In their prospective series of 48 patients, Jastrow and colleagues were able to identify increased levels of IP-10, MIP-1β, IL-10, IL-6, IL-1RA, and eotaxin as predictive of MOF; however, their analysis was focused on four-hour intervals in the first 24 hours following injury (32) as opposed to the four day measurements obtained in our series. Likewise, Maier and coauthors evaluated cytokine concentrations and patterns over 28 days, noting increases in IL-6 and soluble TNF receptors among patients developing as opposed to not developing MOF; but, their series of 344 patients included those with severe traumatic brain injury which has been shown to effect both post-injury cytokine concentration as well as MOF development following trauma (33). Also, in each of these series, different definitions of MOF were utilized, making comparison between the study findings difficult (32, 33).

Our findings are somewhat surprising in that the majority of literature documenting immune dysfunction in the obese patient suggests an existing pro-inflammatory state (8-15, 17, 36). A recent investigation looking at cytokine concentrations in obese patients after laparoscopic cholecystectomy shows that following minor trauma obese patients may have an exaggerated response (37). While our initial belief was that immune hyperactivation due to this pro-inflammatory state would be a potential cause for post-injury complications, our data in fact suggests the contrary, and is more suggestive of a scenario in which the low grade baseline level of inflammation present in the obese actually leads to a diminished response to the stress of severe blunt trauma, which then predisposes these individuals to subsequent infectious complications. Imbalances in cytokine levels have been previously postulated to play a role in this phenomenon. This would support the clinical observations of many previous authors that obese trauma patients are more prone to the development of post-injury infections (20-22, 24, 27, 29, 30, 38), and would be in keeping with recent animal studies in which diet-fed obese mice showed increased susceptibility to *Porpyhromonas gingivalis* and *Staphylococcus aureus* infection relative to lean counterpart animals (39, 40).

Our findings are limited by our study's small sample size and retrospective nature, and as such, we are only able to identify associations between obesity, cytokine concentrations, nosocomial infection development, and MOF without drawing definitive conclusions. Nonetheless, the findings of depressed cytokine elaboration, increased development of nosocomial infections, and significantly later onset of MOF fit with existing animal studies and clinical observations, and are suggestive of a potentially important mechanism in which immune suppression in the obese patient contributes to the development of late post-injury organ failure. Given our findings and those of other authors, further prospective animal and human studies into the issue of post-injury immune dysfunction in the obese patient should be undertaken, as it may provide opportunities for prophylactic and therapeutic interventions in this high risk patient population.

## Conclusions

Despite the documented pro-inflammatory cytokine profile present in obese individuals at baseline, obese patients who have sustained severe injury show a depressed early systemic cytokine response compared to patients of normal BMI. This may suggest an increased susceptibility to nosocomial infection and late MOF. Further study into immune dysfunction in the post-injury obese patient is warranted, and should involve investigation of early immune suppression.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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## Table 1

Study Patient Information

| | **Study Population (n=74)** |
|---|---|
| Age (Years) | 34 ± 11 |
| Gender (Percent Male) | 62% |
| Body Mass Index (kg/m$^2$) | 29 ± 7 |
| Injury Severity Score | 33 ± 14 |
| APACHE II Score | 28 ± 6 |
| Nosocomial Infections | 54% |
| Multiple Organ Failure | 55% |
| Mortality | 8.1% |

Data are presented as means ± standard deviation or as percent having or developing a given condition

**Table 2**

Comparison of Patients with Normal BMI and Obese Patients

| | Normal (n=34) | Obese (n=40) | p-value |
|---|---|---|---|
| Age (Years) | 31 ± 11 | 37 ± 11 | p=0.016 |
| Gender (Percent Male) | 60% | 65% | p=0.760 |
| Body Mass Index (kg/m$^2$) | 23 ± 2 | 35 ± 5 | p<0.001 |
| Injury Severity Score | 35 ± 15 | 31 ± 14 | p=0.271 |
| APACHE II Score | 28 ± 5 | 27 ± 6 | p=0.449 |
| Nosocomial Infections | 45% | 60% | p=0.315 |
| Multiple Organ Failure | 44% | 63% | p=0.178 |
| Mortality (Percent) | 3% | 13% | p=0.209 |

Data are presented as means ± standard deviation or as percent having or developing a given condition

## Table 3

Comparison of Cytokine Concentrations between Normal BMI and Obese Patients

| | Day 0 | | Day 1 | | Day 4 | | |
|---|---|---|---|---|---|---|---|
| | **Normal** | **Obese** | **Normal** | **Obese** | **Normal** | **Obese** | **p-value** |
| IL-4 | 183.8 | 97.7 | 218.8 | 130.3 | 141.5 | 89.6 | 0.025 |
| IL-6 | 241.3 | 200.5 | 242.7 | 107.9 | 86.4 | 52.1 | 0.050 |
| IL-8 | 36.5 | 51.0 | 33.0 | 21.3 | 22.5 | 17.4 | 0.342 |
| IL-10 | 221.6 | 98.5 | 141.0 | 109.2 | 282.0 | 108.9 | 0.006 |
| IFN-γ | 361.0 | 211.5 | 540.2 | 290.0 | 433.1 | 130.2 | 0.061 |
| MCP-1 | 131.6 | 170.7 | 145.6 | 120.3 | 66.0 | 114.0 | 0.372 |
| TNF-α | 18.4 | 16.3 | 30.6 | 11.3 | 20.6 | 9.7 | 0.007 |
| IL-1β | 23.2 | 11.2 | 38.6 | 13.9 | 22.5 | 12.1 | 0.016 |
| CCL-3 | 40.4 | 24.8 | 48.4 | 24.2 | 33.0 | 20.0 | 0.011 |

Data are presented as means, all units are concentrations in pg/mL.