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Differences in outcome between obese and nonobese patients following severe blunt trauma are not consistent with an early inflammatory genomic response

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Abstract

Objectives—Obesity has been demonstrated to alter a number of acute and chronic medical conditions. The effect of obesity on severely injured patients, however, remains incompletely defined. We sought to unravel potential physiologic and genomic alterations induced by obesity in severely injured blunt trauma patients.

Design—A retrospective review of clinical and genomic information contained in the Inflammation and the Host Response to Injury multicenter trauma-related database examining the relationship between body mass index and the early genomic response from peripheral blood leukocytes to patient outcome following severe blunt trauma was performed.

Setting—Multicenter collaboration between university-based academic trauma centers.

Patients—Severely injured blunt trauma patients enrolled in the database.

Interventions—None.

Measurements and Main Results—Univariate analysis of 455 severely injured trauma patients using the National Institutes of Health/World Health Organization body mass index classification system revealed significant increases in morbidity, including longer intensive care unit stays and a greater number of ventilator days, cardiac arrests, episodes of acute renal failure,

and patients developing multiple organ failure. Regression modeling identified body mass index class as being independently associated with adverse outcomes and increased morbidity but an inverse relationship with mortality in patients who suffered severe blunt traumatic injury. Initial leukocyte genomic expression patterns between 163 patients in the four different body mass index groupings did not differ; however, analysis of gene differences between body mass index classes occurring over time demonstrated significant changes in 513 probe sets with significant pathway differences being related to cellular metabolism.

Conclusions—Increasing body mass index is associated with increased morbidity following severe blunt trauma. The initial blood leukocyte inflammatory response to blunt trauma does not appear to differ significantly between patients despite increasing body mass index. Resolution of the inflammatory response may differ between patients on the basis of body mass index; however, additional work is needed to clarify the potential causality of this finding.

Keywords

obesity; trauma; inflammation; genomics; leukocytes

The relationship between increased body weight and risk for disease continues to be a major health concern. The National Institutes of Health has classified individuals according to body mass index (BMI) to assess population-wide risks for comorbid diseases, with persons having a BMI (kg/m²) of 18.5–24.9 normal weight, 25–29.9 overweight, 30–39.9 obese, and >40 morbidly or extremely obese (1, 2). As BMI increases beyond 25, the risk of health complications such as hypertension, hyperlipidemia, diabetes mellitus, cancer, obstructive sleep apnea, pulmonary hypertension, right heart failure, fatty liver disease, osteoarthritis, and renal failure increases (1, 3–9).

Problems associated with overweight or obese patients are not limited to chronic disease. Obesity is also associated with problems in acute illness, such as traumatic injury and subsequent critical care. In fact, several studies have suggested that patients who are heavier suffer increased morbidity following acute injury. Being overweight, obese, or morbidly obese has been associated with increased risks of acute respiratory distress syndrome, acute respiratory failure, acute renal failure, multiple organ system failure (MOF), pneumonia, urinary tract infection, deep vein thrombosis, decubitus ulcer formation, myocardial infarction, and bloodstream infections (10–15). Given these findings, it is not surprising that heavier patients fare worse when using traditional outcome measures such as hospital lengths of stay (LOS), intensive care unit (ICU) LOS, and mechanical ventilation days (10, 12, 14, 16, 17). Despite these effects, there is no consensus that being overweight or obese influences mortality following traumatic injury (10 – 18).

While it is tempting to attribute the adverse outcomes seen in heavier trauma patients solely to logistic issues and abnormal anatomy and physiology, it has been speculated that obesity produces a state of immunologic dysfunction that may contribute to the adverse outcomes seen in this population (10). For example, plasma cytokine derangements have been observed in obese patients, and adipose tissue itself may serve as a source of inflammatory mediators that may dysregulate innate immunity (19–21).

In 2001, the National Institute for General Medical Sciences initiated funding for a multicenter collaborative effort, termed the Inflammation and the Host Response to Injury Large Scale Collaborative Research Program. This “Glue Grant” has created a database containing outcome data from >1000 subjects with severe blunt trauma, and in a subset of 172 subjects the program has collected serial genomic and proteomic data based on whole blood collections. In the present report, we have used both the clinical and genomic databases to evaluate two hypotheses: first, that increasing BMI is an independent risk factor for the development of adverse outcomes (infections, acute respiratory distress syndrome, acute renal failure) in patients with severe blunt trauma and, second, that the overweight, obese, and morbidly obese patient exhibits differences in early inflammatory response, as measured by leukocyte genome-wide expression, that may explain this difference in outcomes.

Materials and Methods

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

Clinical Data Analysis

We performed a retrospective review of the clinical data present in the Inflammation and the Host Response to Injury TRDB. Inclusion criteria for the study population included a) blunt trauma patients with ages between 16 and 55; b) an Abbreviated Injury Scale severity score >2 outside the head region; c) emergency department arrival <6 hrs from the time of injury; d) base deficit >6 or systolic blood pressure <90 mm Hg in prehospital care, or within 60 mins of arrival; e) blood transfusion within 12 hrs of injury; and f) intact cervical spinal cord. Patients were excluded if they a) had a prehospital Glasgow Coma Scale score of <8 or died within the first 48 hrs of hospitalization or b) lacked the information needed to calculate BMI or their BMI was <18.5.

Patients were resuscitated at admission according to a predetermined algorithm based on central venous pressure monitoring (see Supplemental Figure 1, Supplemental Digital Content 1, <http://links.lww.com/CCM/A54>). Supplemental Table 1 contains the mean volumes of fluid and blood products used to resuscitate the patients in the first 12 hours post-injury (see Supplemental Digital Content 2, <http://links.lww.com/CCM/A55>).

Patients were stratified into the National Institutes of Health/World Health Organization BMI categories for comparison. Initially, univariate analyses were performed to compare several characteristics across BMI groups. Continuous data were log transformed, and oneway analysis of variance was used to compare these variables. Pairwise comparison tests were used where appropriate. Chi-square or Fisher's exact tests were used to compare proportional variables. Results were considered significant at $p < .05$.

The same data were used to determine whether increasing BMI represents an independent risk factor for the development of complications. Logistic regression was used to evaluate the effect of BMI on dichotomous dependent variables. For the purposes of these analyses,

BMI class was considered separately with morbid obesity incorporated into the regression as a dummy variable. Age, gender, race, comorbid hypertension, comorbid chronic lung disease, comorbid diabetes mellitus, transfusion of 6 units of packed red blood cells, total volume of fresh frozen plasma transfused, prehospital Glasgow Coma Scale score, Acute Physiology and Chronic Health Evaluation II score, participation in the Inflammation and the Host Response to Injury shock resuscitation standard operating procedure (22), site where clinical care was performed, initial base deficit, and Injury Severity Score (considered as a categorical variable dividing patients into three groups: Injury Severity Score 1–15, 16–25, and >25) were incorporated as covariates in this analysis. Once again, results were considered significant at $p < .05$. Statistics were completed using SPSS 15.0 (SPSS, Chicago, IL).

Genomics Data Analysis

To assess the initial genomic response to severe blunt trauma, we performed a retrospective review of the genomics data present in the Inflammation and the Host Response to Injury TRDB. Patients who lacked BMI data were excluded from analysis; only patients who possessed microarray data for more than one time point and whose microarray RNA quality score was 2 were included. Microarray data for the initial time point (blood draw occurring within 12 hrs of injury) were downloaded from the TRDB Web site (<http://www.gluegrant.org/>) and then normalized using DNA Chip Analyzer 2007 software (dChip, freeware available at <http://www.dchip.org/>). After normalization of microarray data, BRB-ArrayTools software (developed by Drs. Richard Simon and Amy Peng Lam, freeware available at <http://linus.nci.nih.gov/BRB-ArrayTools.html>) was used to perform significance analysis of microarray (SAM) comparison as well as prediction analysis of microarray (PAM) class prediction modeling between traumatically injured patients and 25 healthy volunteer subjects contained in the database. Subsequently, separate SAM and PAM analyses were performed to compare patients at the extremes of BMI (normal vs. morbidly obese), and then multi-class comparisons were completed that compared patients in all four BMI groups. Significance for SAM analysis was determined using a false discovery rate (FDR) of <0.001 with 1,000 permutations of the data set, while significance for PAM analysis was determined using $p < .001$.

Finally, serial individual patient microarrays were divided into seven time groups, roughly corresponding to the following times post injury: 12 hrs, 1 day, 4 days, 7 days, 14 days, 21 days, and 28 days. BRB-ArrayTools was then used to perform a time series analysis using an analysis of variance for mixed effects in which gene expression was considered as a factor of time and BMI. Significance for the time series analysis was set at $p < .001$. In the case of both the static and time series genomic analysis, probe sets that significantly differed were entered into Ingenuity Pathways Analysis version 6 (IPA, Ingenuity Systems, Redwood, CA) for assessment of gene ontology and functionality.

Results

Univariate Clinical Analysis

At the time of the analysis (February 2008), the Inflammation and the Host Response to Injury TRDB contained curated clinical data on 1,002 trauma patients. Limiting this by the outlined inclusion and exclusion criteria resulted in 455 patients who were eligible for further analysis. Division of patients into BMI classification groups established by the National Institutes of Health/World Health Organization identified 173 normal-weight patients, 152 overweight patients, 101 obese patients, and 29 morbidly obese patients. Demographic information is shown in Table 1. Notably, there was a dramatic but not statistically significant increase in mortality in the morbidly obese group.

Comorbidities

Patients who were morbidly obese were found to have more preexisting comorbid conditions compared with their normal-weight counterparts. Specifically, a greater proportion of morbidly obese patients had histories of hypertension (24.1% vs. 6.9%, $p = .006$), chronic lung disease (10.3% vs. 1.2%, $p = .027$), and diabetes mellitus (13.8% vs. 1.2%, $p = .003$). No difference was seen in the frequency of chronic renal disease across patient groups. Statin use was surprisingly low in the population of patients studied, even among the obese and morbidly obese. Only three of the 455 patients were noted to be on statin therapy before their injury.

Resuscitation

On initial presentation, all patient groups had similar hemoglobin concentrations, temperatures, and blood lactate values (data not shown). Normal-weight patients had a slightly worse initial base deficit value than the other groups; however, this was only significant compared with overweight patients (data not shown). Crystalloid and blood product volumes received during the initial 12-hr resuscitation period were similar for all groups (see Supplemental Table 1, Supplemental Digital Content 2, <http://links.lww.com/CCM/A55>); however, normal and overweight patients received more crystalloid and blood product volume per kilogram of body weight than did patients in the obese and morbidly obese groups (data not shown). Responses to the initial resuscitation appeared to differ, as we saw more rapid resolution of the base deficit in normal and overweight patients than in the morbidly obese (Fig. 1).

Outcomes—Clinical Indicators

Differences in hospital LOS, ICU LOS, and ventilator days were examined in the different patient groups (Fig. 2). While there was a stepwise increase in LOS with increasing BMI group and a significant difference was noted on analysis of variance ($p = .028$), no intergroup differences reached statistical significance on pairwise comparison (Fig. 2A). The morbidly obese patients remained in the ICU for a significantly greater period of time than their normal and overweight counterparts (Fig. 2B) and remained on the ventilator more than twice as long (Fig. 2C). There was no effect of sex on outcome.

Complications

The frequencies of both infectious and noninfectious complications were examined. A summary of the complications is presented in Tables 2 and 3. Briefly, there was an increase in nosocomial infections in all groups compared with normal-weight patients, but this was only significant for bloodstream and urinary tract infections. Similarly, there was an overall stepwise increase in the frequency of noninfectious complications that approached, but did not reach, statistical significance. Significant increases were seen in cardiac arrests and acute renal failure, with a nonstatistical trend in acute respiratory distress syndrome and rhabdomyolysis. Finally, the Marshall scoring system (23) was used to assess the development of MOF among groups, with MOF being defined as a Marshall score ≥ 5 . A greater proportion of the obese and morbidly obese developed MOF.

Regression Analysis

Regression modeling was used to assess the association between morbid obesity and the development of complications (Tables 4 and 5). The data were dichotomized to distinguish between the morbidly obese and the other cohorts combined. Briefly, there was an association between the morbidly obese with a number of outcome measures and complications, specifically, MOF, acute renal failure, cardiac arrest, and urinary tract infection. Importantly, logistic regression revealed an inverse association between morbid obesity and mortality.

Genomics Analysis

Microarray data showed that 163 patients met inclusion and exclusion criteria. Division of patients into BMI classification determined by the National Institutes of Health/World Health Organization identified 49 normal-weight patients, 56 overweight patients, 48 obese patients, and ten morbidly obese patients. In addition, the database contained the genome-wide expression data from whole blood leukocytes from 25 healthy, uninjured, volunteer subjects. Using the SAM algorithm, 31,930 probe sets were identified that distinguished the genome-wide expression in the 25 healthy subjects from the entire 163 injured patients at the initial time point, indicating a robust difference in expression between control and injured patients. The PAM algorithm identified 31,692 probe sets and correctly classified the 25 healthy subjects from the injured patients on the basis of gene expression in $>99\%$ of cases (Fig. 3). In contrast, when the gene expression pattern from 49 injured patients of normal weight were compared with gene expression patterns from the ten injured, morbidly obese patients by SAM analysis, no probe sets were found that significantly differed between groups. Likewise, when four-group SAM multiclass comparison was performed, no differences were noted. PAM analysis of gene expression from normal-weight and morbidly obese patients identified 36 probe sets that differed between groups; however, these probe sets were unable to accurately predict the BMI classification of morbidly obese patients using “leave one out” cross-validation schemes (data not shown), indicating an inability to confirm a true association with BMI group. Finally, PAM analysis of patients in all BMI classes identified 42 probe sets that significantly differed across groups. Once again, these were unable to accurately predict BMI classification.

A time series analysis demonstrated 6342 probe sets whose expression differed during the 28-day period among the injured subjects. We found that 513 probe sets differed significantly between BMI classes during this period (see Supplemental Table 2, Supplemental Digital Content 3, <http://links.lww.com/CCM/A56>). Entry of these 513 probe sets into IPA (24) revealed 267 probe sets with known function, among which 222 fit into known canonical pathways. Based on these differences, five distinct canonical pathways emerged as different among patients on the basis of BMI (Table 6). A detailed discussion of these specific pathways is beyond the scope of this report, but differences were identified in three metabolism-related areas, including metabolism of aminosugars, the citric acid cycle, and vitamin D-receptor and retinoid X receptor activation. Additionally, there were significant changes in expression of probe sets related to hepatic injury and fibrosis and cyclic adenosine mono-phosphate-mediated signaling.

Discussion

The present analysis of the Inflammation and the Host Response to Injury database revealed that after severe blunt trauma, obese and morbidly obese subjects have increased frequency of infectious and noninfectious complications. Our outcome data are largely in keeping with the findings of previous investigators in that complications increased with increasing BMI. Our regression analysis supported a BMI effect in the development of some of these complications, supporting the concept of independent associations between BMI and morbidity following trauma. Most importantly, we observed a BMI-related increase in MOF that is consistent with previous observations (10, 12, 14). Although previous reports have shown increases in the development of other complications, such as acute respiratory distress syndrome, pneumonia, deep vein thrombosis, bloodstream infection, and decubitus ulcers (10–14, 16), these were not found to be significant in our series. This is most likely related to the restrictive inclusion and exclusion criteria applied within this study, which precluded the inclusion of elderly patients and patients with severe head injury, who may be more prone to the development of these complications, and which limited sample size. We failed to show an association between increased BMI and mortality, paradoxically finding that morbid obesity was associated with a lower mortality compared with other patient groups *en masse*. We would be hesitant to suggest that morbid obesity is protective against mortality based on this finding, believing rather that the more likely explanation is the overall low mortality rate seen in our series.

While our clinical data add to the body of literature on the effect of obesity in trauma, we further wished to examine the possibility that inflammatory dysfunction associated with increased BMI could be a contributing factor in the more adverse outcomes seen in the obese and morbidly obese patient. This concept is not without precedent, as previous authors have highlighted features present in obese patients who suggest such abnormalities may exist. Hotamisligil et al (25) first noted that tumor necrosis factor- α is overproduced in the adipose tissue and muscle of obese individuals. This study set the stage for subsequent investigations that later demonstrated marked alterations in not only plasma cytokines, such as interleukins-1, interleukin-6, interleukin-8, and interleukin-18, in uninjured obese patients, but also the presence of immune-modulating adipocyte-derived factors like adiponectin and leptin (reviewed in Refs. 21, 26). The presence of this altered cytokine

milieu in the uninjured patient undoubtedly has broad-reaching implications for patient immune function and physiology, and this theory is supported by the link between obesity, excess tumor necrosis factor- α production, and its association with insulin resistance (27).

Our contribution to this topic was based on the hypothesis that perturbations in the blood leukocyte genome, presumably brought about by exposure to the proinflammatory milieu of the obese, would manifest themselves as a differential genomic response to traumatic injury. Presumably, leukocytes obtained from obese patients would exhibit altered baseline genomic expression and would therefore respond differentially to the stress of acute injury. By identifying differences, we proposed that we could discover prognostic factors or targets for modulation in this complication-prone patient population.

In contrast, our evaluation saw no significant differences in initial genomic expression based on BMI. Rather, the findings suggest that the early genomic response is not dependent upon the BMI but more likely reflects the similarity in the overwhelming inflammatory response to the initial injury. This theory is based on the magnitude of change imposed on the leukocyte genome following acute injury being so substantial (>31,000 probe sets) that it likely obscures the more subtle differences that potentially exist between patient groups based on BMI. Although the data set used to complete this analysis is a very robust one compared with those of existing human studies of genome-wide expression, sample size is clearly a limiting factor in this study, and it is possible that with a greater number of samples (particularly in the morbidly obese patient group) expression differences may emerge.

Our evaluation of genomic changes over time suggests that while the initial inflammatory response appeared similar, more subtle differences in genomic response due to BMI did emerge. It is interesting to note that three of the five significantly differing pathways shared the central theme of metabolism, and a fourth (hepatocellular injury and fibrosis) may likewise be associated with metabolic dysfunction. This is suggestive of parallel potential explanations for poorer outcomes in heavier patients. First, underlying nutritional and metabolic abnormalities are known to be present in the obese as part of the metabolic syndrome. These derangements include insulin resistance, glucose intolerance, increased fatty acid turnover, and increased circulation of free fatty acids (reviewed in Ref. 28) and are known to play a part in inflammatory dysfunction in the morbidly obese (29, 30). Second, the adverse clinical outcomes demonstrated in morbidly obese patients in our study and others are those that have been previously been demonstrated in patients with inadequate nutritional support following acute injury (31–33). Our findings exist in concert with these and suggest that nutritional strategies may affect the outcome in this patient population.

The notion that dysfunctional metabolism over time, reflected by the noted changes in the leukocyte genome, is responsible for poorer outcomes as BMI increases is an attractive hypothesis and is reasonable in the context of obesity-related disease; however, given the current limitations of this data set, we cannot conclusively state this. While the expression intensity of 513 probe sets differed, and these differences may represent a varied inflammatory response in obese and morbidly obese patients, it is important to consider that the changes taking place in the leukocyte genome over time are occurring in response not only to the initial traumatic insult but also to other external factors such as infections and

organ dysfunction that occurred during the postinjury time course. As we and others have pointed out, these factors occur at a greater rate in obese and morbidly obese patients. Whether the changes in the genome are the cause or the effect cannot be answered with our data; nonetheless, our data provide a series of novel yet logical targets that warrant further investigation.

Conclusions

Based on the available data, we cannot support the concept that the initial genomic response and, by extension, the initial inflammatory response to injury explain the complications subsequently seen in obese and morbidly obese patients. Our clinical data provide an alternative explanation for the increased rate of complications in the obese and morbidly obese, as a slower return to baseline of base deficit to normal in morbidly obese subjects was observed. This suggests that differences in resuscitative practices using proportionately lower fluid volumes with resultant prolonged cellular ischemia are among the reasons for the morbidity and the late genomic variation seen with increased BMI. While this is but one piece of evidence, it is intriguing enough to warrant further investigation into differences in resuscitative practices that may be altered by differences in BMI. Additionally, our time series analysis provides new insight into temporal inflammatory differences in the obese and morbidly obese trauma patient and offers a relevant new set of targets in the areas of nutrition and metabolism on which to focus research. Given sustained alterations in metabolic acidosis and metabolism, both resuscitation and nutritional support may play important roles in the morbidity associated with morbid obesity. Further investigation is warranted to fully elucidate both the mechanisms responsible and the potential benefits of targeted interventions based on body mass index.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Worst base deficit over time. Patients' worst base deficit was observed over 6-hr time intervals and is compared on the basis of body mass index classification during the first 24 hrs following injury. Values plotted are means. **Significantly worse base deficit for morbidly obese patients compared with patients classified as normal and overweight, $p < .05$.

Figure 2.

Lengths of stay and ventilator days. (A) Patients' mean length of stay, (B) mean length of intensive care unit stay, and (C) mean number of ventilator days are provided for patients in each body mass index classification. Columns represent mean values, with error bars demonstrating 95% confidence intervals. **Significantly greater number of days for morbidly obese patients compared with patients classified as normal and overweight, $p < .05$.

Comparison of Healthy Controls to Injured Patients

Figure 3.

Genome-wide expression in control and traumatically injured patients. An unsupervised analysis of leukocyte genomic expression in 25 control and 163 injured patients within the first 12 hrs following severe blunt trauma was performed and is represented here by heat map with up-regulated genes and down-regulated genes. Hierarchical clustering demonstrates a distinction in total leukocyte genomic expression between healthy control and injured patients.

Table 1**General patient characteristics**

	Normal Weight (n = 173)	Overweight (n = 152)	Obese (n = 101)	Morbid (n = 29)	p
Mean age, yrs	30	34	36	34	<.001
Percent male	54.3	77	60.4	58.6	<.001
Mean Injury Severity Score	27	27	25	27	.251
Mean Acute Physiology and Chronic Health Evaluation II Score	25	25	25	28	.301
Percent mortality	6.3	4.6	5.0	17.2	.070

Table 2

Nosocomial infections (%)

	Normal Weight (n = 173)	Overweight (n = 152)	Obese (n = 101)	Morbid (n = 29)	p
Any nosocomial infection	41.0	48.0	42.6	62.1	.150
Pneumonia	26.6	28.1	26.7	31.0	.958
Bloodstream infection	8.1	15.0	19.8	13.8	.043
Urinary tract infection	17.9	12.4	14.9	34.5	.028
Catheter-related bloodstream infection	2.9	3.9	5.0	10.3	.301
Ventilator-associated pneumonia	25.9	23.7	25.7	20.7	.915

Values are percentages.

Table 3

Noninfectious complications (%)

	Normal Weight (n = 173)	Overweight (n = 152)	Obese (n = 101)	Morbid (n = 29)	p
Any noninfectious complication	36.4	38.8	46.5	58.6	.078
Acute respiratory distress syndrome	20.2	21.1	27.7	41.4	.053
Cardiac arrest	2.3	2.6	2.0	17.2	<.001
Myocardial infarction	0.0	1.3	1.0	3.4	.253
Cerebral infarction	2.9	2.0	3.0	0.0	.765
Deep vein thrombosis	5.2	5.9	6.9	6.9	.941
Pulmonary embolism	2.3	3.9	3.0	3.4	.868
Rhabdomyolysis	1.2	5.2	4.0	10.3	.053
Acute renal failure	1.2	0.0	2.0	10.3	<.001
Multiple organ failure	43.9	46.7	58.4	72.4	.008

Values are percentages.

Table 4
Body mass index class relationship between morbidly obese and other cohorts in regards to general complications

	Odds Ratio	95% Confidence Interval	<i>p</i>
Nosocomial infections	2.124	0.865–5.216	.100
Noninfectious	2.076	0.833–5.177	.117
complications Mortality	0.198	0.048–0.818	.025

Table 5
Body mass index class relationship between morbidly obese and other cohorts in regard to specific complications

	Odds Ratio	95% Confidence Interval	<i>p</i>
Multiple organ failure	2.876	1.005–8.226	.049
Acute respiratory distress syndrome	2.141	0.846–5.418	.108
Cardiac arrest	16.361	3.528–75.879	<.001
Myocardial infarction	0.042	0.000–82.620	.413
Stroke	0.000	0.000–infinity	.998
Deep vein thrombosis	0.932	0.180–4.825	.933
Pulmonary embolism	3.656	0.372–35.889	.266
Rhabdomyolysis	3.214	0.698–14.811	.134
Acute renal failure	13.035	1.604–105.94	.016
Pneumonia	1.072	0.420–2.733	.885
Bloodstream infection	1.124	0.331–3.811	.851
Catheter-related bloodstream infection	3.982	0.823–19.273	.086
Urinary tract infection	3.374	1.277–8.912	.014
Ventilator-associated pneumonia	0.649	0.228–1.847	.417

Table 6
Significant canonical pathways and differentially expressed probe sets from analysis of variance for mixed effects of body mass index over time

Pathway	Hepatic Fibrosis/Hepatic Stellate Cell Activation	Cyclic Adenosine Monophosphate-Mediated Signaling	Aminosugars Metabolism	Citrate Cycle	Vitamin D ₃ Receptor/Retinoid X Receptor Activation
Significance, <i>p</i>	.023	.026	.031	.032	.034
Probe sets/total	7/131	8/159	4/104	3/59	5/80
Probe sets	Fibroblast growth factor 1 Insulin-like growth factor binding protein 5 IL-1 receptor, type 1 IL-1 receptor, type 2 Matrix metalloproteinase-9 Myosin light chain 9 SMAD-3	Adenosine A3 receptor Angiotensin II receptor, type 2 Calcium/calmodulin dependent protein kinase I Calcium/calmodulin dependent protein kinase ID Phosphodiesterase 11A Phosphodiesterase 3A Phosphodiesterase 4D	Phosphodiesterase 11A Phosphodiesterase 3A Phosphodiesterase 4D Phosphodiesterase 7A	Citrate lyase-β like Fumarate hydratase Succinate dehydrogenase complex	CCAAT/enhancer binding protein-β Forkhead box O1 Hairy and enhancer of split 1 IL-2 Insulin-like growth factor binding protein 5

IL, interleukin.