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Plasma adiponectin and mortality in critically ill subjects with acute respiratory failure

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Abstract

Objective—Adiponectin, an anti-inflammatory cytokine produced by adipose tissue, has been shown to modulate survival in animal models of critical illness. We examined the association between plasma adiponectin and clinical outcomes in critically ill patients with acute respiratory failure.

Design—Secondary analysis of a single-center, randomized controlled trial.

Setting—Medical intensive care unit of a university-based, tertiary medical center.

Patients—One hundred seventy-five subjects with acute respiratory failure enrolled in randomized, controlled pilot trial of trophic vs. full-caloric enteral feeding (EDEN pilot study).

Interventions—None.

Measurements and Main Results—Adiponectin measured within 48 hrs of respiratory failure (Apn1) was inversely correlated with body mass index ($r = -0.25$, $p = .007$) and was higher in females (median, 12.6 $\mu\text{g/mL}$; interquartile range, 7.6–17.1) than males (9.45 $\mu\text{g/mL}$; 6.2–14.2; $p = .02$). Adiponectin increased at day 6 (Apn1: 11.4 $\mu\text{g/mL}$ [6.6–15.3] vs. Apn6: 14.1 $\mu\text{g/mL}$ [10.3–18.6], $p < .001$). This increase was significant only in survivors (Δ adiponectin in survivors: $3.9 \pm 6 \mu\text{g/mL}$, $n = 80$, $p < .001$ vs. Δ in nonsurvivors: $1.69 \pm 4.6 \mu\text{g/mL}$, $n = 14$, $p = .19$). Higher Apn1 was significantly associated with 28-day mortality (odds ratio 1.59 per 5- $\mu\text{g/mL}$ increase; 95% confidence interval 1.15–2.21; $p = .006$). No measured demographic, clinical, or cytokine covariates, including interleukin-6, interleukin-8, interleukin-10, interleukin-1 β , interleukin-12, tumor necrosis factor- α , and interferon- γ , were confounders or effect modifiers of this association between adiponectin and mortality.

Conclusions—Independent of measured covariates, increased plasma adiponectin levels measured within 48 hrs of respiratory failure are associated with mortality. This finding suggests that factors derived from adipose tissue play a role in modulating the response to critical illness.

Keywords

adiponectin; respiratory insufficiency; critical illness; biologic markers; epidemiology; translational research

Acute respiratory failure requiring support with mechanical ventilation occurs with an incidence of 77–102 per 100,000 person-years, accounts for 40–55% of patients admitted to intensive care units, and is associated with 30–40% mortality (1–3). The inflammatory sequelae of severe infection—sepsis and acute lung injury—represent common causes of acute respiratory failure (1–3). Although many cytokine mediators of the innate immune response have been investigated as potential prognostic biomarkers of sepsis and acute lung injury (4–7), few mediators have been shown to accurately predict clinical outcomes in acute respiratory failure.

Adipose tissue has been increasingly recognized as an important endocrine organ (8). Adipocytokines are factors released from adipose tissue that act on distant tissues to regulate a wide variety of immune and metabolic processes. Adiponectin, the most abundant immunologically active protein secreted into the blood by adipose tissue, has been shown to play an important role in vascular homeostasis, insulin sensitivity, and immune regulation (8). The predominant role of adiponectin in immune regulation appears to be as an anti-inflammatory molecule. For example, adiponectin has been shown in culture to inhibit baseline activation and block agonist-induced inflammation in macrophages (9), T cells (10), and endothelial cells (11). Consistent with these findings, adiponectin-deficient mice have been demonstrated to have activated macrophages, increased circulating levels of proinflammatory cytokines, and a propensity to develop spontaneous lung inflammation (12–14). Additionally, adiponectin-deficient mice have an increased inflammatory response and decreased survival in polymicrobial sepsis resulting from cecal ligation and puncture (15, 16).

To date, the role of adiponectin in human critical illness has not been extensively investigated. In recent reports (17–19), circulating adiponectin levels were found to be lower in critically ill patients during the acute phase of illness when compared with healthy control subjects or subjects recovering from critical illness. Taken together, these studies suggest that low plasma adiponectin would be associated with adverse outcomes in critical illness.

The primary objective of the present study was to investigate the relationship between plasma adiponectin levels and clinical outcomes in critically ill patients with acute respiratory failure.

MATERIALS AND METHODS

Subjects

Data were collected from the 200 subjects enrolled in the trial, Timing of Target Enteral Feeding in the Mechanically Ventilated Patient (NCT00252616), conducted at Vanderbilt University Hospital (Nashville, TN). This trial was the pilot study intended to provide logistic and sample size information to inform conduct of the multicenter ARDSNet EDEN trial. The Boston University School of Medicine Institutional Review Board approved the present *post hoc* study that used deidentified data collected as part of the trial. The methods and clinical outcomes of this trial, which was approved by Vanderbilt Institutional Review Board and for which all subjects or their surrogates provided informed consent, have been previously presented in abstract form (20).

The EDEN pilot trial was a single-center, randomized controlled, trial comparing initial low-volume, “trophic” with early full-caloric enteral feedings in critically ill, mechanically ventilated patients. The trial included subjects with acute respiratory failure who were expected to require mechanical ventilation for >72 hrs and whose physicians had intent to feed enterally. Subjects were excluded from the EDEN pilot study for the following reasons: age <13 yrs, time >48 hrs since initiation of mechanical ventilation, absence of informed consent, patient or care team not committed to full medical support, estimated survival <24 hrs or prior conditions present with >50% estimated 28-day mortality, refractory shock, cirrhosis with Child-Pugh score >10, bowel obstruction or infarction, severe malnutrition with body mass index (BMI) <18.5 kg/m² or >30% loss of total body weight in the previous 6 months, enterocutaneous fistula, total parenteral nutrition use, neuromuscular disease impairing spontaneous respiration, inability to raise the head of bed to 45°, or allergy to the enteral formula.

The following clinical and demographic covariates were collected at the time of enrollment into the EDEN pilot study: age, gender, weight, height, BMI, reason for intensive care unit admission, race, severity of illness (Acute Physiology and Chronic Health Evaluation [APACHE] II score); and presence of comorbid conditions (diabetes, cardiac disease, chronic obstructive pulmonary disease, chronic renal failure, chronic liver disease, malignancy, immunosuppression, or acquired immunodeficiency syndrome). The initial level of positive end-expiratory pressure, presence or absence of shock, and blood values of glucose, platelets, creatinine, and bilirubin were documented.

Plasma for measurement of baseline adiponectin (Apn1) was available from 185 of 200 (92.5%) of the subjects enrolled in the pilot trial. Ten of these subjects were excluded from these analyses of adiponectin: eight with BMI <18.5 kg/m² (protocol exclusion violation), one with Apn1 >3 sds above the mean, and one with patient height >3 sds below the mean. Thus, 175 subjects, of which 35 died before day 28, are included in the subsequent analyses.

Plasma Measurements

As part of the EDEN pilot trial, two 10-mL EDTA blood tubes were collected from each subject at each of two time points: 1) study enrollment (day 1), which was within 48 hrs of initiation of mechanical ventilation; and 2) day 6 after enrollment. Specimens were centrifuged and frozen at -70°C. Adiponectin, leptin, and insulin were measured by enzyme-linked immunosorbent assays at the Boston University laboratory (Otsuka Pharmaceuticals, San Francisco, CA; and Lincoplex human gut hormone kit, Linco Research, Inc, St Louis, MO), whereas interferon- γ , tumor necrosis factor- α , interleukins (IL)-1 β , IL-6, IL-8, IL-10, and IL-12 were measured at the Vanderbilt Laboratory using standard enzyme-linked immunosorbent assays.

Clinical Outcomes

The primary clinical outcome for the present study was 28-day mortality. A secondary clinical outcome measure was ventilator-free days (VFDs) (21). VFDs are calculated as the number of days out of the first 28 after randomization that a subject is both alive and free from mechanical ventilation.

Statistical Analyses

Continuous variables were non-Gaussian and were log-transformed for graphic presentation. Untransformed data were assessed with Spearman rank correlation coefficients, Wilcoxon rank sum, or Kruskal-Wallis tests, as appropriate; adiponectin levels were presented as medians and interquartile ranges (IQRs). Because no currently accepted clinically relevant cutoffs or normal ranges have been defined for adiponectin, for clarity of data presentation,

baseline covariates were stratified by quartile of Apn1 level. The quartiles for Apn1 were as follows: quartile 1, <6.5 µg/mL, quartile 2, 6.6–11.4 µg/mL, quartile 3, 11.5–15.3 µg/mL, and quartile 4 >15.3 µg/mL.

Associations of 28-day mortality with plasma adiponectin levels were quantified using odds ratios with 95% confidence intervals (CIs) from multiple logistic regression models. As secondary outcome analyses, death and VFDs were modeled as a survival-time function using Cox proportional hazards models and Kaplan-Meier curves. Hazard ratios and 95% CIs were computed from the Cox models. The proportional hazards assumption was tested through entry of an interaction term for time and adiponectin level into the models; all Cox proportional hazards models met the proportional hazards assumption. Three models were constructed for adiponectin–outcome relationships: 1) an unadjusted analysis; 2) an *a priori* analysis including the variables of age, APACHE II score, gender, BMI, and EDEN pilot study intervention group; and 3) an analysis constructed only of covariates shown to be confounders, ie, those that changed the odds ratio of the unadjusted model by >10%. Predefined analyses were performed to assess for effect modification of any association between adiponectin and mortality by including an interaction term for etiology of respiratory failure (acute lung injury or sepsis vs. no acute lung injury or sepsis). The discriminating power of measured variables as predictors of mortality was determined by measuring the area under the receiver operating curve. Model calibration was determined using Hosmer-Lemeshow testing; all reported models showed adequate Hosmer-Lemeshow calibration with $p > .05$.

All analyses were conducted with SAS version 9.1 (Cary, NC) with an α level of 0.05.

RESULTS

Association of Adiponectin With Clinical and Demographic Characteristics

Apn1 was inversely correlated with BMI ($r = -0.25$, $p = .007$; Table 1; Fig. 1). No other continuous baseline variable correlated with Apn1, including platelets, age, APACHE II, height, creatinine, bilirubin, F_{IO_2} , ratio of the partial pressure of arterial oxygen to F_{IO_2} (PaO_2/F_{IO_2}), minute ventilation, positive end-expiratory pressure level, or plasma leptin and insulin levels (see Supplemental Table 1; Supplemental Digital Content 1, <http://links.lww.com/CCM/A176>). Apn1 was significantly lower in male subjects than in female subjects (9.45 µg/mL [IQR, 6.2–14.2] vs. 12.6 µg/mL [7.6–17.1]; $p = .02$). No differences in Apn1 were found among categories of etiology of respiratory failure, medical history, race, presence of shock on admission, or pilot trial intervention group.

Day 1 Adiponectin as a Predictor of Mortality

Median Apn1 was lower in survivors (10.35 [IQR, 5.9–15.0]) than in nonsurvivors (14.1 [IQR, 9.1–17.7]; $p = .007$; Fig. 2). Higher Apn1 was associated with an increased odds ratio (OR) of 28-day mortality (OR, 1.59 per 5-µg/mL increase; 95% CI, 1.15–2.21; $p = .0056$; Fig. 3). After adjustment for potential confounders defined *a priori* (age, APACHE II score, gender, BMI, and EDEN pilot study intervention group), the association between Apn1 and mortality was not changed (OR, 1.54; $p = .018$). In fact, no confounders or effect modifiers, including etiology of respiratory failure (p for interaction .18), of the association between adiponectin and mortality were identified. Survival analysis of Apn1 and mortality produced similar results to the logistic regression models (hazard ratio, 1.40; 95% CI, 1.09–1.81; $p = .009$; Fig. 4).

Additional bivariate predictors of 28-day mortality were age (OR, 1.028; 95% CI, 1.006–1.050; $p = .012$), APACHE II (OR, 1.058; 95% CI, 1.007–1.11; $p = .026$), nonwhite race (2.86; 95% CI, 1.14–7.14; $p = .026$), and the presence of shock at enrollment (2.38; 95% CI,

1.15–4.88; $p = .019$). After adjustment for APACHE II, racial differences in mortality disappeared, replicating previously described observations (22).

Including all five variables associated with mortality in the bivariate analyses together in a multiple regression model demonstrated that only Apn1 (OR, 1.49 per 5- μ g/mL; 95% CI, 1.06–2.11) and age (OR, 1.04 per year; 95% CI, 1.01–1.06) were independently associated with 28-day mortality. Apn1 area under the receiver operating curve (0.65) was higher than that of all other predictors, including APACHE II (0.62).

Adiponectin and VFDs

Similar to mortality, increased adiponectin levels were associated with fewer days alive and free from mechanical ventilation. VFDs decreased with higher Apn1 (hazard ratio, 0.80; 95% CI, 0.68–0.94; Fig. 5A). This effect was explained by the relationship between Apn1 and mortality because differences between Apn1 and VFDs were not significant among survivors (hazard ratio, 0.93; 95% CI, 0.8–1.1; $p = .39$; Fig. 5B).

Day 6 Adiponectin and Mortality

Of the 175 patients with an Apn1 measurement, 95 had an Apn6 measurement. Plasma adiponectin increased significantly from enrollment to day 6 (Apn1, 11.4 μ g/mL IQR 6.6–15.3 vs. Apn6, 14.1 μ g/mL IQR 10.3–18.6; $p < .001$; Fig. 2). This increase in adiponectin (Δ adiponectin) was significant only in survivors (Δ adiponectin in survivors 3.9 ± 6 , $n = 80$, $p < .001$; Δ in nonsurvivors 1.69 ± 4.6 , $n = 14$, $p = .19$; Fig. 2). Unlike Apn1, the association between Apn6 and 28-day mortality was not statistically significant (OR 1.28 per 5- μ g/mL increase Apn6; 95% CI, 0.84–1.97; $p = .26$). Furthermore, after controlling for Apn1, Δ adiponectin was not significantly associated with mortality (OR, 0.92; 95% CI, 0.53–1.57).

Adiponectin and Other Cytokines

Apn1 was significantly correlated with IL-10 ($r = .157$, $p = .04$, $n = 171$) but not with other measured cytokines (see Supplemental Table 1; Supplemental Digital Content 1, <http://links.lww.com/CCM/A176>). Entering the measured cytokines as covariates in the regression models did not change the significant relationship between adiponectin and mortality.

DISCUSSION

This study investigated the association between plasma adiponectin levels and clinical outcomes in critically ill subjects requiring mechanical ventilation. The major finding in this study was that high serum adiponectin levels were found to correlate with increased 28-day mortality. This association persisted after adjustment for potentially confounding covariates and was preserved across all diagnostic categories in our study sample. Remarkably, adiponectin levels measured within 48 hrs of initiating mechanical ventilation performed as well as APACHE II in predicting mortality.

To our knowledge, these results are the first to demonstrate an association between adiponectin and mortality in critically ill patients. This finding is concordant with clinical studies of adiponectin levels in other conditions such as acute coronary syndrome (23) and dyspnea (24) that have noted a direct association between adiponectin and mortality. At present, it is unclear whether adiponectin plays a direct role in influencing clinical outcomes in these conditions.

The kinetics and range of plasma adiponectin levels measured in the present study were similar to those observed in prior published reports of adiponectin during acute illness (17–19, 23, 25). Together, studies demonstrate that adiponectin levels are low early in critical

illness and begin to rise by day 6. In addition, our study observed that the increases in adiponectin levels from day 1 to day 6 were attenuated in nonsurvivors. This may suggest that the normal response to critical illness is an acute decrease in plasma adiponectin levels with a gradual increase in adiponectin during recovery. Because no study has longitudinally measured adiponectin levels during the transition from a state of health into acute illness, we cannot confirm whether an initial drop in adiponectin levels occurs early in critical illness. However, the normal range of plasma adiponectin in men from the Health Professionals Follow Up cohort (median, 16.5 $\mu\text{g/mL}$; IQR, 11.6–22.9) (26) appears to be substantially higher than the levels measured from our male subjects early in acute respiratory failure (9.45 $\mu\text{g/mL}$; IQR, 6.2–14.2); adiponectin levels in our subjects approach the normal range by day 6 (13.2 $\mu\text{g/mL}$; IQR, 10.1–19.4). We speculate that the higher day 1 adiponectin levels of nonsurvivors represent a dysfunctional adiponectin response to critical illness. Although these data need to be interpreted with caution because of the limited numbers of samples analyzed on day 6, results suggest that monitoring changes in adiponectin levels may be useful for identifying “at-risk” patients with respiratory failure in the intensive care unit.

Clinical observations that demonstrate a positive correlation between adiponectin and mortality appear to differ from results of animal studies. Experimental models in mice have consistently shown a relationship between low adiponectin states (ie, knockout mice) and poor outcomes. For example, adiponectin knockout mice produce greater amounts of proinflammatory cytokines and experience greater mortality after cecal ligation and puncture-induced sepsis; these findings are attenuated after adiponectin supplementation before initiation of sepsis (15, 16). The observed differences between human and murine studies cannot easily be explained; however, others have speculated that increased adiponectin during acute illness represents a compensatory response to an acute proinflammatory state or to resistance at the level of adiponectin receptors (27, 28).

Another significant finding in this study was that serum adiponectin did not correlate with levels of circulating proinflammatory cytokines (tumor necrosis factor- α , interferon- γ , IL1- β , IL-6, IL-8, IL-12) but was associated with the antiinflammatory cytokine IL-10. These data suggest adiponectin plays less of a role in proinflammatory responses to critical illness and is more involved in processes related to the resolution of inflammation, a hypothesis supported by the rise in adiponectin in survivors later during the course of critical illness. Importantly, the addition of IL-10 to regression models did not alter the relationship between adiponectin and mortality. These findings intimate that anti-inflammatory activities of adiponectin and IL-10 are mediated through separate and distinct signaling pathways; this is supported by recent *in vitro* data demonstrating adiponectin and IL-10 act independently to suppress human macrophage activation (29).

Importantly, our study replicated the well-published findings of both an inverse relationship between adiponectin levels and BMI and lower adiponectin levels in men (23, 26). Unlike prior studies investigating changes in adiponectin with insulin therapy (17, 18), we did not find a correlation between adiponectin and plasma insulin or glucose levels; we did not capture data on exogenous insulin administration.

Analyses of secondary outcomes demonstrated that VFDs also decreased as ApnI increased. VFDs are a composite outcome of survival and ventilator days used to attenuate bias that may occur in measuring ventilator days alone if patients experience early mortality while requiring mechanical ventilation. In examining the results of survivors alone, who are not prone to this bias from early death, the time on the ventilator was not different by adiponectin quartile. Thus, the differences in VFDs with increasing adiponectin levels are explained by increased mortality and not duration of respiratory failure.

We recognize the limitations to this study. First, data were derived from a single-center, randomized controlled trial, so it is unclear if results can be generalized to other populations or to other critically ill patients not requiring mechanical ventilation. However, the consistency of the relationship between adiponectin and mortality across multiple diagnostic categories suggests results may be widely applicable to a broad range of patients. Second, because the investigation of the relationship between adiponectin and mortality was not the intent of the EDEN pilot trial, potentially important covariates such as information related to insulin administration were not recorded for these subjects. Third, adiponectin measurements were not available in 15 subjects, three of whom were nonsurvivors. It is impossible to know if data obtained from these patients would have altered our results. Finally, results related to changes in adiponectin from enrollment to day 6 should be interpreted with caution given the possibility that characteristics of patients with missing data may have introduced selection bias.

CONCLUSION

In summary, this study demonstrates that plasma adiponectin levels are independently associated with mortality in a heterogeneous population of critically ill patients with respiratory failure. We show that lower adiponectin levels early in the course of critical illness are associated with improved survival. These findings suggest that adiponectin plays an important role in modulating the response to critical illness and provide support for future investigations examining the functional role of adiponectin and other adipocytokines during critical illness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Association between natural log-transformed body mass index (*BMI*) and plasma adiponectin, $r = -0.22$, $p = .028$.

Figure 2.

Box plots of plasma adiponectin at study enrollment and study day 6 stratified by 28-day vital status. Adiponectin levels at enrollment were significantly lower in survivors than nonsurvivors. Additionally, the increase in adiponectin from enrollment to day 6 was statistically significant only in survivors.

Figure 3. Association between increasing adiponectin quartile and 28-day mortality; p for trend .01.

Figure 4.

Association between plasma adiponectin and 28-day survival. Subjects with adiponectin levels measured at study enrollment that were below the median had significantly improved survival compared with those with adiponectin above the median; log rank $p = .018$.

Figure 5.

Ventilator-free survival by enrollment adiponectin quartile for all subjects (*A*) and survivors only (*B*). Ventilator-free survival improved with low adiponectin levels for all subjects (*A*), log-rank $p = .03$. However, ventilator-free days were not different between adiponectin quartiles when only survivors were analyzed, log-rank $p = .66$.

Table 1

Baseline demographics and clinical characteristics

Baseline Variables (mean ± sd or no. [%])	Entire Cohort (n = 175, Unless Otherwise Specified)	Quartile of Baseline Adiponectin, µg/mL			
		1 (<6.5) (n = 42)	2 (6.6–11.4) (n = 46)	3 (11.5–15.3) (n = 44)	4 (>15.3) (n = 43)
Age, years	53.8 ± 17.5	50.4 ± 20	54.5 ± 15	54.0 ± 18	56.4 ± 17
Sex, ^a male	76 (43.4)	21 (50)	25 (54)	18 (41)	12 (28)
Race, white	157 (90)	36 (86)	44 (96)	39 (89)	38 (88)
Body mass index, ^a kg/m ²	29.2 ± 9.3	32 ± 9.3	27.7 ± 7.4	31.0 ± 12	26.2 ± 6
Respiratory failure etiology					
Acute lung injury	37 (21)	5 (12)	11 (23)	10 (22)	11 (26)
Altered mental status	32 (18)	8 (19)	7 (15)	10 (22)	7 (16)
Pneumonia	31 (18)	6 (14)	8 (17)	8 (18)	9 (21)
Sepsis	19 (11)	5 (12)	6 (13)	1 (2)	7 (16)
COPD/respiratory failure NOS	15 (8.5)	6 (14)	2 (4)	4 (9)	3 (7)
Stroke	5 (2.8)	2 (5)	3 (7)	0 (0)	0 (0)
Aspiration	5 (2.8)	2 (5)	2 (4)	0 (0)	1 (2)
Cardiac arrest	5 (2.8)	0 (0)	2 (4)	1 (2)	2 (5)
Other (incidence <5)	26 (15)	8 (19)	5 (11)	9 (20)	2 (5)
APACHE II	26.8 ± 7.2	26 ± 7.4	27.9 ± 7.2	26 ± 6.5	27.4 ± 7.6
Presence of shock	70 (40)	14 (33)	22 (48)	14 (32)	20 (47)
Creatinine, mg/dL	1.8 ± 1.4	1.4 ± 1.1	1.9 ± 1.4	1.9 ± 1.9	1.9 ± 1.3
Platelets, $\times 10^3/\mu\text{L}$	216 ± 128	225 ± 102	170 ± 103	230 ± 163	244 ± 124
Minute ventilation, L/min, n = 161	9.2 ± 3.0	8.9 ± 2.6	9.8 ± 3.4	9.0 ± 3.2	9.0 ± 2.4
Positive end-expiratory pressure, cm H ₂ O	7.8 ± 3.7	8.1 ± 3.9	7.5 ± 3.6	7.1 ± 3.1	8.7 ± 4.2
Percent of inspired O ₂	51 ± 17	53 ± 17	49 ± 17	52 ± 18	52 ± 16
Glucose mg/dL	149 (68)	159 (72)	153 (68)	135 (57)	158 (74)
Trophic feeding intervention	88 (50)	22 (52)	25 (54)	20 (45)	21 (49)

COPD, chronic obstructive pulmonary disease; NOS, not otherwise specified; APACHE, Acute Physiology and Chronic Health Evaluation.

^a $p < .05$ for a trend with increasing adiponectin quartiles;

$p = .03$ for difference between quartile 2 and quartile 4 only.