Insulin resistance in critically ill patients with acute renal failure

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Hyperglycemia associated with insulin resistance is a metabolic/hormonal derangement that has been the subject of recent investigation in critically ill patients with multiorgan failure. Van den Berghe et al. (30) recently showed that intensive insulin therapy designed to maintain blood glucose at or below 110 mg/dl reduces morbidity and mortality among critically ill patients in a surgical intensive care unit. We hypothesized that insulin resistance, defined by hyperglycemia in the setting of hyperinsulinemia, would be highly prevalent and associated with increased mortality in critically ill patients with ARF. We also hypothesized that the insulin-like growth factor (IGF) pathway, a critical component of insulin action, would be active in this process.

MATERIALS AND METHODS

Study design. This paper contains an analysis of data from the Program to Improve Care in Acute Renal Disease (PICARD). The PICARD study was a prospective cohort study examining the natural history, practice patterns, and outcomes of treatment in critically ill patients with ARF, conducted at five academic medical centers in the United States1 from February 1, 1999 to August 31, 2001. A detailed report regarding the spectrum of ARF in the complete PICARD study can be found elsewhere (9). The study was approved by the Institutional Review Board of each participating hospital, and informed consent was obtained from all study participants or their next-of-kin. The study was conducted in accordance with the guidelines of the Declaration of Helsinki.

Study population. All adult (age ≥18 yr) ICU patients with ARF in whom a nephrology service consultation was received were considered for the study. Six hundred and eighteen patients were enrolled in the PICARD study. As a substudy, patients enrolled at Vanderbilt University Medical Center (VUMC) and Maine Medical Center (MMC) were asked to undergo measurements of biomarkers of inflammation and insulin resistance. A total of 414 ARF cases from these two centers were initially evaluated, with 201 (49%) meeting entry criteria for PICARD. This particular study required an additional consent form, which 98 patients/next-of-kin agreed to sign. Of these 98 patients, 90 (73 at VUMC, 17 at MMC) had data obtained on inflammation and insulin resistance. Patients were followed prospectively from the time of initial nephrology service consultation until death or hospital discharge. Renal function was assessed daily from records of urine output, blood urea nitrogen (BUN), and serum creatinine. RF was defined as an increase in serum creatinine ≥44

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μmol/l (≥0.5 mg/dl) with baseline serum creatinine <133 μmol/l (<1.5 mg/dl), or an increase in serum creatinine ≥88 μmol/l (≥1.0 mg/dl) with baseline serum creatinine ≥133 μmol/l (1.5 mg/dl) and <442 μmol/l (5.0 mg/dl). Patients with a baseline serum creatinine ≥442 μmol/l (5.0 mg/dl) were not considered for study inclusion.

Exclusion criteria included having previous dialysis, kidney transplantation, ARF from urinary tract obstruction or from hypovolemia responsive to fluids, as well as being a prisoner or pregnant patient.

Study parameters. The study consisted primarily of measurements of serum insulin, IGF-I, and IGF binding protein (IGFBP) and -3 within 48 h of the initial nephrology consultation. Daily determinations of glucose were obtained from the patient's medical records, beginning at the time of nephrology consultation and each day thereafter over the course of hospitalization. If more than two glucose concentrations were obtained during a 24-h period, the value obtained closest to 8 AM was recorded. There were very few patients who had data available by the end of week 5 (n = 14), due to death, transfer out of the ICU, or resolution of ARF. Therefore, the glucose data were censored at week 5. Glucose measurements were also examined in the larger PICARD cohort. Of the 618 patients in the PICARD study, 509 had glucose data available for analysis.

Demographic data (i.e., age, sex, race), vital signs, hemodynamic data (where available), and general laboratory data were recorded for the first ICU day and each day from the time of nephrology consultation, and generic severity-of-illness scores were computed from these variables. At the time of initial nephrology assessment, patients were evaluated for the presence of systemic inflammatory response syndrome (SIRS), sepsis, or septic shock as defined by American College of Chest Physicians/Society of Critical Care Medicine guidelines. Specifically, SIRS was defined as the systemic inflammatory response to an unspecified stimulus manifested by the presence of two or more of the following: 1) a body temperature >38°C or <36°C; 2) a heart rate >90 beats/min; 3) on a ventilator, or tachypnea, manifested by a respiratory rate >20 breaths/min, or hyperventilation, as indicated by a PaCO₂ of <32 Torr; and 4) a white blood cell count >12,000/μm³ or <4,000/μm³, or the presence of >10% immature neutrophils. Sepsis included the above criteria when an infectious source was documented or strongly suspected. Septic shock was defined as sepsis with hypotension despite adequate fluid resuscitation, along with the presence of perfusion abnormalities.

Patients were classified with or without diabetes based on past medical history. Information on total parenteral nutrition (TPN), enteral feeding, or insulin administration was obtained from the patient’s medical chart.

Analytic procedures. Baseline venous samples of serum insulin, serum IGF-I, and serum IGFBP-1 and -3 were collected into EDTA tubes and clot activator tubes for plasma and serum separation, respectively, within 48 h of nephrology consultation. Samples were immediately centrifuged, and the plasma and serum were stored at −70°C until analysis. Serum samples were measured in duplicate by ELISA, using kits from DSL Laboratories (Webster, TX). The detectable limits and interassay coefficients of variation were 0.03 μU/ml and 7% for insulin, 0.26 μg/l and 9% for IGF-I, 0.25 μg/l and 8% for IGFBP-1, and 0.04 μg/l and 11% for IGFBP-3, respectively (www.dslabs.com).

Statistical analysis. Continuous data were described as means ± SD or median with interquartile range and compared with Student’s t-test or the Wilcoxon rank sum test, where appropriate. Correlations among inflammatory markers, proteins in the IGF-IGFBP axis, insulin levels, nutritional markers, and severity of illness scores were calculated using the Spearman (rank-based) correlation coefficient. Categorical variables were described as proportions and compared with Fisher’s exact test. We compared concentrations of markers of insulin resistance (insulin and glucose levels) and proteins in the IGF-IGFBP axis (IGF-I, IGFBP-1 and -3) between survivors and nonsurvivors and patients with and without diabetes. We used linear regression to assess the effect of TPN on glycemic control. We used logistic regression to evaluate the odds of death associated with concentrations of insulin, IGF-1, IGFBP-1 and -3 and glucose (time averaged over 1 wk), adjusting for age, sex, race, diabetes, degree of renal dysfunction (whether hemodialysis was required), and nutritional status (using prealbumin as a proxy for visceral protein stores). To obviate linearity assumptions, we ranked the population into quartiles and compared the odds of death relative to the first quartile. To determine whether glycemic control was associated with mortality, we averaged daily glucose measurements over each week of hospitalization. Glucose trends among survivors and nonsurvivors were also compared using the mixed model procedure (15, 16). All tests of significance were two-sided, and differences were considered statistically significant at P < 0.05. The statistical software SAS version 8.2 (Cary, NC) was used for data analyses.

RESULTS

Patient characteristics. The demographic and clinical characteristics for the 90 patients at the time of nephrology consultation are summarized in Table 1. The mean age (±SD) of the total study population was 59.6 ± 15.9 yr, with 59% male and 96% Caucasian. One-third of the patients (32%) had diabetes, and one-third of patients (33%) had preexisting hypertension.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Age, yr</th>
<th>59.6 ± 15.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>53 (59)/37 (41)</td>
<td></td>
</tr>
<tr>
<td>Race (Caucasian/African American)</td>
<td>86 (96)/4 (4)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>29 (32)</td>
<td></td>
</tr>
<tr>
<td>ARF on CRI</td>
<td>29 (32)</td>
<td></td>
</tr>
<tr>
<td>History of cardiac disease</td>
<td>37 (41)</td>
<td></td>
</tr>
<tr>
<td>History of liver disease</td>
<td>16 (18)</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>47 (52)</td>
<td></td>
</tr>
<tr>
<td>Sepsis, septic shock, or SIRS</td>
<td>34 (38)</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Patient demographics and clinical features of study population at the time of nephrology consultation

| Severity of illness scores | APACHE II | 23.1 ± 6.5 |
| APACHE III | 63.8 ± 22.1 |
| SAPS II | 30.0 ± 14.3 |
| SOFA | 5.5 ± 2.7 |

Values are presented as means ± SD (n = 90 patients) or no. of cases and (%). Information on chronic renal insufficiency (CRI) available on 89 patients, coronary artery disease (CAD; 83 patients), surgery (83 patients), sepsis (83 patients), blood urea nitrogen (BUN; 79 patients), creatinine (80 patients), urine output (86 patients), organ system failure (80 patients), and severity of illness scores (87 patients) is shown. ARF, acute renal failure; SIRS, systemic inflammatory response syndrome; APACHE, acute physiology and chronic health evaluation; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment.
chronic kidney disease. The predominant etiology of ARF based on clinical presumption was ischemic (46%) or multifactorial acute tubular necrosis (41%). The mean (±SD) BUN and creatinine at the time of nephrology consultation were 21.8 ± 10.7 mmol/l and 283 ± 115 μmol/l, respectively, median urine output was 908 ml (interquartile range 342–1,605)/24 h: 30% of patients were oliguric (daily urine output <400 ml) at the time of consultation. Fifty-seven percent of the patients received renal replacement therapy during the course of their illness. Among patients with diabetes, 17 (59%) received insulin while in the ICU; none of the patients without diabetes received ICU insulin. In terms of nutritional supplementation while in the ICU, 42 (46.5%) of patients received enteral feeds, 7 (8%) received TPN, 26 (29%) received both, and 15 (16.5%) received no nutritional support. Of the 15 patients who received no nutritional support, 2 (13%) were NPO and 13 (87%) were prescribed food ad libitum.

One hundred three patients from VUMC and MMC were included in PICARD but declined to participate in this sub-study (“nonparticipants”), of which data were available on ninety-eight. Nonparticipants were slightly older than study participants (64.8 ± 14.1 vs. 59.6 ± 15.9 yr, P = 0.02). However, there were no significant differences in sex, race/ethnicity, history of diabetes mellitus, or renal parameters, including serum creatinine, BUN, and presence of oliguria, at the time of consultation in the two groups. A similar fraction in both groups underwent renal replacement therapy over the course of the study. The acute physiology and chronic health evaluation (APACHE) III scores were higher among nonparticipants compared with participants (84.5 ± 19.7 vs. 76.8 ± 17.8, respectively, P = 0.009). Conversely, the simplified acute physiology scores were higher in the participants compared with the nonparticipants (53.6 ± 14.7 vs. 41.7 ± 12.8, respectively, P < 0.001).

Overall survival. The overall all-cause mortality rate in this study population was 43%. Eighty-seven percent of the deaths occurred in the ICU. Nonsurvivors were more likely to be oliguric than survivors (47.4 vs. 16.7%, P = 0.002) and more likely to be dialyzed (76.9 vs. 41.2%, P = 0.001).

Glucose levels. Changes in glycemic control during hospitalization were examined and compared among survivors and nonsurvivors in the subcohort of 90 patients (Fig. 1). Glucose levels in survivors were lower than in nonsurvivors throughout the 5-wk period (P = 0.008). Glucose concentrations were significantly higher in patients with diabetes, as expected. The association between survival and better glycemic control was independent of diabetes status, as well as age, sex, race, severity of illness, plasma cortisol level, severity of ARF (whether the patient required hemodialysis), and nutritional status (adjusted P = 0.013).

To validate these results, glucose levels were also examined in the larger PICARD cohort. Five hundred nine patients had glucose levels available for analysis (Fig. 2). After an adjustment for age, sex, diabetes, severity of ARF, and severity of illness, mean glucose concentrations among survivors were lower than among nonsurvivors throughout the 5-wk period (P < 0.0001, adjusted P = 0.0006). Analysis was adjusted for age, sex, diabetes, severity of renal failure, and severity of illness.

Insulin levels. The mean serum insulin concentration was significantly higher among nonsurvivors compared with survivors (431 ± 508 vs. 234 ± 189 pmol/l, P = 0.03, Table 2). When insulin concentrations were divided into quartiles, the higher quartiles were associated with significantly increased relative odds of death (Fig. 3). The effect of supplemental nutrition on glycemic control was also examined. In this study, neither TPN (P = 0.99) nor enteral feeding (P = 0.61) was significantly associated with glycemic control.

Fig. 1. Glucose trends in survivors vs. nonsurvivors in subset of 90 patients over 5 wk. Glucose levels in survivors were lower than nonsurvivors throughout the 5-wk period (P = 0.008, adjusted P = 0.013).

Fig. 2. Glucose trends in survivors vs. nonsurvivors, larger Program to Improve Care in Acute Renal Disease study (n = 509). Glucose concentrations among survivors were lower than among nonsurvivors throughout the 5-wk period (P < 0.0001, adjusted P = 0.0006). Analysis was adjusted for age, sex, diabetes, severity of renal failure, and severity of illness.

Fig. 3. Risk profile for glucose level in quartiles (n = 509). The analysis was adjusted for demographics, renal function, and severity of illness (P = 0.025). Values in histogram bars represent median baseline glucose values of the respective quartiles (in mmol/l).
Table 2. Levels of serum insulin and proteins in the IGF-IGFBP axis in survivors vs. nonsurvivors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors (n = 51)</th>
<th>Nonsurvivors (n = 39)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin, pmol/l</td>
<td>234±189*</td>
<td>431±508</td>
<td>0.030</td>
</tr>
<tr>
<td>IGFL1, µg/l</td>
<td>114±46.7</td>
<td>103±42.4</td>
<td>0.270</td>
</tr>
<tr>
<td>IGFBP1, µg/l</td>
<td>61.7±60.2</td>
<td>86.2±77.1</td>
<td>0.056</td>
</tr>
<tr>
<td>IGFBP3, µg/l</td>
<td>1,470±581*</td>
<td>1,190±498</td>
<td>0.021</td>
</tr>
<tr>
<td>Week 1 glucose, mmol/l</td>
<td>8.4±2.8</td>
<td>9.9±4.7</td>
<td>0.096</td>
</tr>
<tr>
<td>HOMA-R</td>
<td>11.7±12.5*</td>
<td>24.1±30.0</td>
<td>0.038</td>
</tr>
<tr>
<td>Cortisol</td>
<td>48.6±41.4</td>
<td>44.8±34.1</td>
<td>0.696</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 90. Significant P values are in bold. *P < 0.05 vs. nonsurvivors.

Table 3. Levels of serum insulin, glucose, and proteins in the IGF-IGFBP axis in diabetic vs. nondiabetic patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diabetic (n = 29)</th>
<th>Nondiabetic (n = 61)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin, pmol/l</td>
<td>244±179</td>
<td>357±436</td>
<td>0.095</td>
</tr>
<tr>
<td>IGFL1, µg/l</td>
<td>98.9±42.0</td>
<td>114.6±45.7</td>
<td>0.122</td>
</tr>
<tr>
<td>IGFBP1, µg/l</td>
<td>90.1±78.0</td>
<td>64.0±63.0</td>
<td>0.147</td>
</tr>
<tr>
<td>IGFBP3, µg/l</td>
<td>1,270±526</td>
<td>1,380±576</td>
<td>0.372</td>
</tr>
<tr>
<td>Week 1 glucose, mmol/l</td>
<td>10.9±4.2*</td>
<td>8.2±3.3</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 90. Significant P values are in bold. *P < 0.01 vs. nondiabetic patients.

used for this calculation was drawn on the same day as the insulin concentration had been drawn. The median and interquartile range of HOMA-R in this study population was 9.47 (4.10–18.81). The mean HOMA-R level was significantly higher among nonsurvivors than survivors (24.1 ± 30.0 vs. 11.7 ± 12.5, P = 0.04). Although HOMA-R was significantly associated with mortality in the univariate analysis, it lost its significance when adjusted for other variables. Those patients who required hemodialysis had higher HOMA-R levels (22.4 ± 28.1 vs. 11.1 ± 11.3, P = 0.04). The mean HOMA-R level was unassociated with length of stay in the ICU (P = 0.52), and was unrelated to acidosis (P = 0.10) or inflammatory markers such as IL-1β, IL-6, IL-8, IL-10, or TNF-α (P > 0.09 for all comparisons).

IGF-IGFBP axis. IGFBP-3 levels were lower in nonsurvivors than in survivors (1,190 ± 498 vs. 1,470 ± 581 µg/l, P = 0.02, Table 2). There was a trend toward higher IGFBP-1 levels in nonsurvivors compared with survivors (86.2 ± 77.1 vs. 61.7 ± 60.2 µg/l), although this difference did not quite reach statistical significance (P = 0.056). These three variables were not significantly different in patients with and without diabetes (Table 3).

Predictors of mortality. Logistic regression was used to examine possible predictors of mortality. Variables examined included age, sex, race, APACHE III score, glucose concentrations over the 5 wk, severity of ARF (whether hemodialysis performed), nutritional status (prealbumin), and supplemental nutrition received by the patient. The best predictors of mortality were severity of ARF (P < 0.001), glucose concentration (P = 0.017), prealbumin concentration (P < 0.001), and APACHE III score (P = 0.006).

DISCUSSION

This study was designed to examine insulin resistance in a population of critically ill patients with ARF. We show that hyperglycemia over a period of 5 wk may be associated with mortality and that insulin levels were higher in those who died. The hyperglycemia observed among our patients may be a reflection of the process of insulin resistance. This hypothesis is supported by the separate significant associations of higher blood glucose concentrations, higher insulin concentrations, and higher HOMA-R scores with increased mortality. Among these, hyperglycemia was an independent predictor of death even after adjustment of severity of illness scores, cortisol (as a marker of hormonal stress), and other patient-related conditions that may influence the outcome of interest. Insulin concentration was drawn on the smaller 90-patient subset and as a one-time measurement, which may explain why it did not have an independent association with mortality, as was seen with hyperglycemia. These findings suggest that insulin resistance may contribute to the high mortality risk consistently observed among critically ill patients with ARF.

Among the many metabolic disturbances seen in critical illness, abnormalities in glucose metabolism have been the focus of recent investigation. Finney et al. (11) performed an observational study of critically ill patients and found that those with better glucose control had lower mortality. They investigated the focus of recent investigation. Finney et al. (11) performed an observational study of critically ill patients and found that those with better glucose control had lower mortality. They investigated the

Fig. 4. Risk profile for insulin level in quartiles in subset of 90 patients (unadjusted P = 0.03). Values on histogram bars represent median baseline insulin values of the respective quartiles (in pmol/l).
more likely to develop insulin resistance due to the effects of loss of kidney metabolic function in addition to insulin resistance from critical illness. Several lines of evidence suggest that the kidney plays an important role in glucose homeostasis (1, 8, 19, 27, 28). Observations in humans during euglycemic hyperinsulinemic clamp experiments strongly suggest that insulin suppresses renal glucose production (8, 25). Since glucose homeostasis in the kidney is regulated by insulin, loss of kidney metabolic function could account for a component of insulin resistance due to loss of a major target organ for insulin action. Uremia is also associated with decreased hepatic and peripheral glucose uptake, and it has additionally been reported that adipocytes from partially nephrectomized uremic rats have a decreased number of glucose transporters (14). Thus multiple lines of evidence in human and animal studies point to the importance of the kidney in glucose homeostasis and as a potent contributor to insulin resistance.

Whether both hyperglycemia and hyperinsulinemia or one of them contributes directly to adverse events in critically ill patients with ARF or is simply a marker of metabolic injury severity has not been adequately established. However, a number of studies in both human and animal models suggest that hyperglycemia and hyperinsulinemia may exert profound effects on the acute inflammatory response and oxidative stress pathways, which are also important predictors of outcome in critically ill patients with ARF (2, 7, 12, 13, 17, 22–24, 26). Interestingly, we found no significant associations among insulin resistance and a wide array of pro- and anti-inflammatory cytokine concentrations. Similarly, insulin resistance was unrelated to the degree of acidosis or cortisol concentrations.

Another potential mechanism is that hyperinsulinemia, independently of hyperglycemia, may have mitogenic actions, which can cause excessive proliferation of arterial smooth muscle cells, leading to vascular injury. It is not known whether this deleterious effect of insulin occurs in the setting of critical illness or ARF.

Finally, insulin resistance may influence outcome through alterations in the IGF-1 and IGFBP axis in the critical illness setting. The IGF-IGFBP axis exerts insulin-like actions, and changes in the levels of proteins in this axis alter insulin resistance. IGFBP-1, one of six binding proteins for IGF-1, has been used as a marker of hepatic insulin sensitivity (with elevated levels indicating insulin resistance) and has been studied in critical illness (20). Mesoten et al. (20) found high IGFBP-1 levels in critically ill patients, which were believed to reflect increased insulin resistance and were higher in those who died. IGFBP-3, another binding protein for IGF-1, carries the majority (90–95%) of circulating IGF-1 in a ternary complex consisting of IGF-1, IGFBP-3, and an acid-labile subunit (3). Timmins et al. (29) detected a protease directed against IGFBP-3 and found that IGFBP-3 levels were low in critically ill patients. In critical illness, the increased IGFBP-3 proteolysis, which would decrease IGFBP-3 levels and increase IGF-1 bioavailability, may be an attempt to counteract insulin resistance. Therefore, low IGFBP-3 levels could reflect increased insulin resistance. Our results are consistent with this hypothesis, as IGFBP-3 was significantly lower, and IGFBP-1 was higher, among ARF patients who died. Future therapies to improve insulin resistance and improve outcomes in this patient population should take into consideration the involvement of the IGF-IGFBP axis in this metabolic process (4, 20).

An interesting finding of the study was that there were no significant differences in the levels of insulin, IGF-1, and the binding proteins among patients with or without diabetes. One can speculate on a few possible reasons for these results. First, the sample size is very small, with only 29 patients with diabetes. Second, the diagnosis of diabetes was based on information available in the medical records. Thus some of the insulin-resistant patients might have had non-insulin-dependent diabetes that was not noted. Third, the data indicate that all of the patients in the study, on average, had some level of insulin resistance, as defined by hyperglycemia and hyperinsulinemia. This may be related to their critical illness and possibly their renal failure. All of these factors could have masked the differences among diabetic and nondiabetic patients.

The present study has several limitations. Most of the data were obtained at one time point, which was measured at the time of nephrology consultation. Ideally, repeated measurements of these variables should be done to better understand the fluctuations that would occur during the ICU stay. However, to our knowledge, there are no studies in the literature that have published repeated measurements of all these variables in critically ill patients with ARF. The results of this study should lead to future studies with better design to explore the associations between the markers of metabolic derangements observed in this patient population. Another limitation of this study is that the use of HOMA-R as a measure of insulin resistance may not be the most sensitive measurement of insulin resistance. A better approach, although more logistically difficult, may have been the use of hyperinsulinemic-euglycemic clamp studies. The length of time that patients were critically ill before the nephrology consultation varied among patients. This variability might have affected the IGFBP-1 data because this protein is initially high early in critical illness, but subsequently decreases (5). It should be noted that there are virtually no studies that have systematically examined time-dependent variations in metabolic and hormonal derangements in critically ill patients with ARF, and the present report provides a compelling rationale for such a study. This study sample of the PICARD cohort was also nearly all Caucasian. While in general African Americans and other race/ethnicity groups are underrepresented in similar cohorts, they might demonstrate different relationships among the variables described. Because all PICARD patients were in the ICU at the time of consultation, we are unable to comment on the relationship among these variables and mortality in patients with less severe ARF, or the unlikely subjects with severe ARF but who are otherwise healthy.

As with all observational studies, the associations described do not allow for casual inference. This particular study generates intriguing hypotheses that should lead to clinical trials required to determine whether intensification of glycemic control or other interventions aimed at these metabolic pathways will reduce mortality (or nonrecovery of renal function) in this population.

In conclusion, our results suggest that insulin resistance may be associated with mortality in critically ill patients with ARF. IGFBP-3 is significantly lower, and IGFBP-1 is higher, in patients who died. The IGF-IGFBP axis may play an important role in the abnormal control of the insulin signaling pathway in patients with ARF.
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DISCLOSURES

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REFERENCES