COVID-19–Associated Acute Kidney Injury and Quantified Protein Catabolic Rate: A Likely Effect of Cytokine Storm on Muscle Protein Breakdown

Jaime Uribarri, Osama El Shamy, Shuchita Sharma, and Jonathan Winston

Rationale & Objectives: Previously we reported a cohort of patients with coronavirus disease 2019 (COVID-19)–associated acute kidney injury (AKI) with striking biochemical evidence of tissue breakdown in the absence of apparent rhabdomyolysis. We sought to quantify the extent of tissue catabolism in similar patients.

Study Design: During acute peritoneal dialysis (PD) in patients with COVID-19–associated AKI, we measured urea Kt/V adequacy and calculated the daily urea nitrogen generation rate while quantifying daily protein intake.

Setting & Population: We did calculations in 8 patients with COVID-19–associated AKI undergoing acute PD at Mount Sinai Hospital in New York City. As a comparator, we obtained urea kinetic parameters from our database of ambulatory patients receiving maintenance PD.

Exposure or Predictors: 8 patients with COVID-19–associated AKI undergoing acute PD.

Outcomes: Urea nitrogen generation rate in relation to daily protein intake.

Analytical Approach: Urea nitrogen generation rate from urea kinetics was related to measured daily dietary protein intake in these patients and we compared it with this relationship in ambulatory maintenance PD patients for whom both parameters were calculated from urea kinetics.

Results: Urea nitrogen generation rate in patients with AKI was 10.2 ± 5 g/d, which is more than 2-fold higher than for stable outpatients receiving maintenance PD (4.7 ± 3 g/d) despite similar dietary protein intake (74.8 ± 11 vs 67.2 ± 29 g/d, respectively). This strongly suggests endogenous protein breakdown, probably from muscle. Urea nitrogen generation rate in these patients with AKI corresponds to 315 g/d of ongoing muscle breakdown and cumulative 2.5 kg of muscle breakdown during the early course of AKI.

Limitations: Small number of participants and assumptions in comparing urea nitrogen generation rate with protein intake.

Conclusions: In highly catabolic patients, an endogenous source of urea generation such as muscle protein breakdown seems to be the most likely explainable cause for our findings. This is the first study that we are aware of to quantify the degree of endogenous protein breakdown induced by COVID-19–related cytokine storm.

During the peak of the coronavirus disease 2019 (COVID-19) pandemic in the greater New York area, acute kidney injury (AKI) was identified as a major complication of the disease. We have previously reported on a subset of patients with AKI, a high number of critically ill patients in the intensive care unit with striking biochemical evidence of tissue breakdown, a metabolic state typically characteristic of tumor lysis syndrome or rhabdomyolysis. All patients had COVID-19–related pneumonia with respiratory failure and AKI, but none had cancer or high creatine kinase levels. We postulated that the catabolic state was part of the COVID-19 cytokine storm.

In view of the increasing number of patients requiring dialysis for both acute and chronic kidney disease, many nephrologists were faced with obstacles to meeting dialysis demands, including staffing and supply shortages, as well as dialysis circuit thrombosis. Acute peritoneal dialysis (PD) became a valuable alternative for dialyzing patients with AKI, and we previously described the implementation of an acute PD program in our institution.

We report on our assessment of dialysis adequacy in some of our acute PD patients. By simultaneously estimating urea generation rate, we demonstrate a striking degree of protein breakdown, most likely of muscle origin, in these critically ill coronavirus-infected patients, supporting our clinical impression of a highly catabolic state. We believe that this is the first such report to quantify the extent of muscle breakdown in a COVID-19–related cytokine storm.

METHODS

Dialysis adequacy by urea Kt/V was measured when feasible in all patients with COVID-19 with AKI who received acute PD while inpatients at Mount Sinai Hospital in New York City during April 2020. We report on all 8 of these patients in whom we were able to demonstrate stability of both serum creatinine and serum urea nitrogen (SUN) levels for at least 2 days before urine and PD effluent sample collections. Urea and creatinine kinetics were assessed simultaneously as part of Kt/V estimation (Adequest software; Baxter, Inc).

All these patients developed AKI in the setting of COVID-19–related pneumonia and experienced marked increases in serum creatinine, SUN, and phosphate levels at...
In a rate faster than usual for AKI. Anion gap metabolic acidosis with normal lactate levels and rapid decreases in serum albumin levels were also seen (Table 1). Together, these biochemical parameters were consistent with a hypercatabolic state, similar to what we have previously described in a different contemporaneous cohort of patients.2

Urea nitrogen and creatinine concentrations were measured in 24-hour urine and PD effluent samples obtained during the patients’ admission by the hospital clinical laboratory.6

The following calculations were then made: (1) dialysis urea nitrogen generation (g/d): dialysate urea nitrogen concentration (g/L) × 24-hour PD effluent volume (L); (2) urinary urea nitrogen generation (g/d): urinary urea nitrogen concentration (g/L) × 24-hour urine volume (L); and (3) total urea nitrogen generation (g/d): urinary urea nitrogen generation + dialysate urea nitrogen generation. The same equations were used to calculate total creatinine generation in g/d but replacing urea nitrogen with creatinine concentration.

Total body water (TBW) was then estimated depending on the patient’s sex. For men, TBW = actual body weight (kg) × 0.6. For women, TBW = actual body weight (kg) × 0.5. Weekly urea Kt/V = [24-hour urinary + dialysate urea clearance (in L/d)] × 7 TBW.

To contextualize and compare the resultant urea and creatinine kinetics, we reviewed the database of maintenance PD patients from our outpatient home dialysis unit. From a total of 80 maintenance PD patients, we matched 8 control patients for age, sex, and weight (see Table 2).

Protein intake in g/d for the acute PD cohort was calculated directly from dietary information of the enteral feeding solutions and/or supplemented by oral food protein content reported in the nutritionists’ notes in patients’ electronic medical records. For the control group, protein intake was estimated as is standard practice from the urea nitrogen generation rate based on the Randall formula.

Baxter’s Adequest software was used for estimating dialysis adequacy (Kt/V) and urea nitrogen and creatinine generation rates.6

All statistical analyses were performed using SPSS (IBM, Armonk, NY) version 26.0 software. We used the Kolmorov-Smirnov test to define normal distribution. All values were expressed as mean ± standard deviation, except for creatine kinase. Statistical significance between the mean values was established using unpaired t test or 1-way repeated-measures analysis of variance depending on the number of groups. P < 0.05 was considered statistically significant.

This study was approved by the Institutional Review Board (approval number: 20-00533) at the Icahn School of Medicine at Mount Sinai. The need for informed consent was waived because of deidentified information.

RESULTS

General Characteristics of the Study Population

Of the 8 acute PD patients, 50% were men, mean age was 59 ± 10 years, weight was 94.4 ± 26 kg, and body mass index was 33 ± 7.7 kg/m². Table 1 shows laboratory data for these patients before the initiation of any form of dialysis. Of note, at that point in time, on the average 6 days after the initial increase in serum creatinine level, mean SUN level was 150 mg/dL and serum phosphorus level was 9.8 mg/dL. Average creatine kinase level was 200 (range, 72-830; reference, 30-200) U/L. In 5 of the 8 patients (63%), hemodialysis or continuous kidney replacement therapy had failed before being switched to PD.

Table 1. Average Serum Laboratory Values Before Initiation of Any Form of Dialysis in Our Cohort of 8 Patients With AKI

| Serum Parameter          | Mean ± Standard Deviation |
|--------------------------|----------------------------|
| Serum urea nitrogen, mg/dL | 150 ± 26                   |
| Creatinine, mg/dL        | 11.2 ± 4.5                 |
| Potassium, mEq/L         | 5.4 ± 1.2                  |
| Bicarbonate, mEq/L       | 16.5 ± 2.5                 |
| Calcium, mg/dL           | 8.2 ± 1.2                  |
| Phosphorus, mg/dL        | 9.8 ± 2.7                  |
| Lactate, mmol/L          | 1.5 ± 0.8                  |
| Anion gap, mEq/L         | 23.4 ± 7.0                 |
| Albumin, g/dL            | 2.05 ± 0.87                |

Note: Values were obtained before initiation of any form of dialysis in these patients. It took an average of 6 days from initial increase in serum creatinine level to initiation of dialysis. Conversion factors for units: serum urea nitrogen in mg/dL to mmol/L, ×0.357; creatinine in mg/dL to μmol/L, ×88.4; calcium in mg/dL to mmol/L, ×0.2495; phosphorus in mg/dL to mmol/L, ×0.3229. Abbreviation: AKI, acute kidney injury.

Kidney Med Vol 3 | Iss 1 | January/February 2021

**Table 2.** Match Parameters Between Acute Patients and Controls

| Parameter | Matched Control Patient | Matched Acute Patient |
|-----------|-------------------------|-----------------------|
| Age (years) | 61 ± 19                 | 61 ± 24               |
| Sex (male) | 4                     | 4                     |
| Weight (kg) | 94 ± 28                | 94 ± 26               |

**Table 3.** Urea Nitrogen Generation Rates

| Calculation | Rate (g/d) |
|-------------|------------|
| Dialysate   | 7.7        |
| Urinary     | 5.0        |
| Total       | 12.7       |

**Table 4.** Creatinine Clearance Rates

| Calculation | Rate (mg/dL) |
|-------------|--------------|
| Dialysate   | 7.7          |
| Urinary     | 5.0          |
| Total       | 12.7         |
Table 2. Comparing Baseline Characteristics and Urea Kinetics of Both Acute and Maintenance PD Patients

| Parameters                              | Acute PD | Maintenance PD | P    |
|----------------------------------------|----------|----------------|------|
| Age, y                                  | 59 ± 10  | 58 ± 12        | 0.95 |
| Weight, kg                              | 94.4 ± 26| 92.5 ± 24      | 0.88 |
| Body mass index, kg/m²                  | 33.0 ± 7.7| 33.4 ± 6.4     | 0.92 |
| Sex (male:female)                       | 4:4      | 4:4            |      |
| Serum urea nitrogen, mg/dL              | 100.4 ± 33| 55.2 ± 12      | 0.01 |
| Serum creatinine, mg/dL                 | 6.3 ± 5.2| 10.7 ± 3.2     | 0.09 |
| Total urea nitrogen generation, g/d     | 10.2 ± 5 | 4.7 ± 3        | 0.03 |
| Total creatinine generation, g/d        | 0.9 ± 0.4| 1.0 ± 0.8      | 0.66 |
| Protein intake, g/d                     | 74.8 ± 11| 67.2 ± 29      | 0.52 |
| Weekly urea Kt/V                        | 1.7 ± 1.0| 2.1 ± 0.5      | 0.36 |

Note: Maintenance PD patients were selected from a population of 80 maintenance PD patients matched for age, sex, and weight with the 8 acute PD patients. P values were established using unpaired t test. Abbreviation: PD, peritoneal dialysis.

Serum Creatinine and SUN Levels Immediately Before the Study

Serum creatinine and SUN levels were stable in the 2 days before the urine and PD effluent collections. SUN level was 99 ± 33.6 mg/dL on day 1, 100.2 ± 31.3 mg/dL on day 2, and 100.4 ± 33 mg/dL on the day of collection (P = 0.8926). Similarly, serum creatinine values were 6.3 ± 5 mg/dL on day 1, 6.5 ± 5 mg/dL on day 2, and 6.4 ± 5 mg/dL on the day of collection (P = 0.85).

General Characteristics of the Control Population

The matched maintenance PD counterparts were 50% men, mean age was 58 years, weight was 92.5 kg, and body mass index was 33.4 kg/m² (Table 2). Mean SUN level in the end-stage kidney disease group was half that of the study group (55.2 vs 100.4 mg/dL).

Estimation of Urea Nitrogen Generation Rate

Estimated daily protein intake was not different (74.8 vs 67.2 g/d, respectively), as was dialysis dose (weekly Kt/V, 1.7 vs 2.1, respectively). The urea nitrogen generation rate in patients with AKI was more than double that in the maintenance group (10.2 vs 4.7 g/d, respectively). The urea generation rate in controls (the maintenance PD patients) was not different from values in our entire outpatient PD cohort (n = 80; 4.7 ± 3 vs 5.2 ± 2.5 g/d, respectively).

DISCUSSION

In this study, we sought to quantify our clinical observation that some patients with COVID-19 with AKI have marked tissue breakdown, as is suggested clinically by rapid increases in SUN, creatinine, uric acid, and phosphorus levels. By leveraging the clinical information obtained when assessing PD adequacy, we proved this by demonstrating a much higher rate of urea nitrogen generation than can be explained by daily dietary protein intake. This becomes especially clear when these patients are compared with a cohort of age-, sex-, and weight-matched patients with end-stage kidney disease receiving maintenance PD. This excessive urea nitrogen generation indicates an endogenous source that most likely comes from muscle protein breakdown. We are not aware of any other study that has quantitated the extent of tissue breakdown in this hypercatabolic state.

The urea kinetics calculations for the maintenance PD cohort, based on the Adequest program, suggest that daily urea nitrogen generation is only 7% of daily protein intake, which fits other balance studies in maintenance PD showing that daily urea nitrogen generation is ~8% of a daily protein intake of ~75 g. If we extrapolate these data, the excess urea nitrogen generation of ~5 g/d in our acute patients would have required an endogenous protein breakdown of ~63 g/d (assuming that 8% of protein is converted into urea nitrogen). Because ~20% of muscle is protein, this would translate into the loss of ~315 g of muscle each day, an impressive amount. This is on top of the initial amount of protein breakdown required to increase the SUN level from normal (~20 mg/dl) to 100.4 mg/dL. This difference in SUN levels of 80.4 mg/dL over an average TBW of our cohort of 50 L would have required the addition of ~40 g of urea nitrogen, derived from 500 g of protein or 2.5 kg of muscle mass. This extremely large amount of protein breakdown not only confirms the hypercatabolic clinical presentation in these patients but also may very well be contributing to morbidity and mortality.

We have previously postulated that this hypercatabolic state is another manifestation of the cytokine storm syndrome, well described in COVID-19–associated pulmonary complications. Both interleukin 6 and tumor necrosis factor α have a direct effect on muscle protein breakdown and there is a growing body of literature supporting their role in muscle wasting associated with chronic inflammation, HIV infection, and cancer. This likely contributes to the laboratory result abnormalities observed in our patients that have traditionally been described as catabolic. These abnormalities are classically found in rhabdomyolysis and tumor lysis syndrome, neither of which was present in our previously described cohort of patients with COVID-19–associated AKI.

This study has several limitations. The most important may be that urine and PD fluid collections were not done under optimal conditions in a metabolic unit. Our participants were critically ill patients in a hospital, crowded with a tremendous influx of COVID-19–infected patients. We ensured the stability of SUN and serum creatinine levels for 2 days before fluid collections but it may be argued that a longer period of stabilization might have been necessary to estimate the urea nitrogen generation rate. There was simply no...
opportunity to optimize the patients’ conditions and wait until a well-demonstrated steady state had been reached.

Another limitation may be that the assumption of a urea nitrogen generation rate of 8% of the source protein is based on data from maintenance dialysis patients and may not apply in this acute condition. We would argue that even if the actual numbers are not exactly right, they undoubtedly document a significant magnitude of protein catabolism.

A third limitation may be that the hypercatabolic state may not be exclusively COVID-19 induced but associated with treatments associated with acute respiratory failure. One of our patients received an average daily dose of intravenous methylprednisolone of 40 mg/d for a few days. This only partially explains the mentioned hypercatabolism in that particular individual, but steroids cannot be the explanation in the rest of the cohort. We cannot entirely eliminate contribution from other agents, such as investigational drugs such as remdesivir, but any study agents in this critically ill patient group were individualized and not representative of the group.

We believe that our study provides insight into the hypercatabolic state of patients diagnosed with COVID-19–associated pneumonia and hopefully presents a roadmap for future further investigations and tailoring of our treatment approaches in these patients.

ARTICLE INFORMATION

Authors’ Full Names and Academic Degrees: Jaime Uribarri, MD, Osama El Shamy, MD, Shuchita Sharma, MD, and Jonathan Winston, MD.

Authors’ Affiliations: Division of Nephrology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY (JU, SS, JW); and Division of Nephrology and Hypertension, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN (OES).

Address for Correspondence: Jaime Uribarri, MD, Icahn School of Medicine, Division of Nephrology, One Gustave L. Levy PI, PO Box 1243, New York, NY 10029. E-mail: jaime.uribarri@mountsinai.org

Authors’ Contributions: Research idea and study design: JW, JU; data acquisition: OES, JU; data analysis/interpretation: SS, OES, JW, JU; statistical analysis: JW, JU; supervision or mentorship: JW, JU. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Support: None.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Acknowledgements: The authors acknowledge the hard work and dedication of the Mount Sinai Home Dialysis Unit PD nursing staff for their extraordinary efforts, without which none of this would have been possible.

Peer Review: Received July 10, 2020. Evaluated by 2 external peer reviewers, with direct editorial input from the Statistical Editor and the Editor-in-Chief. Accepted in revised form September 13, 2020.

REFERENCES

1. Chan L, Chaudhary K, Saha A, et al. Acute kidney injury in hospitalized patients with COVID-19. Preprint. Posted online May 8, 2020. medRxiv. https://doi.org/10.1101/2020.05.04.20090944.
2. Patel N, Rein JL, Sanchez-Russo L, et al. COVID-19 associated acute kidney injury: a case series. Kidney Med. 2020;2:668-669.
3. Wilson FP, Berns JS. Onco-nephrology: tumor lysis syndrome. Clin J Am Soc Nephrol. 2012;10:1730-1739.
4. Petjeova N, Martinek A. Acute kidney injury due to rhabdomyolysis and renal replacement therapy: a critical review. Crit Care. 2014;18:224.
5. Goldfarb DS, Bernstein JA, Zhdanova O, et al. Impending shortages of kidney replacement therapy for COVID-19 patients. Clin J Am Soc Nephrol. 2020;15:880-882.
6. El-Shamy O, Patel N, Halim Abdelbaset M, et al. Acute start peritoneal dialysis during the COVID-19 pandemic: outcomes and experiences. J Am Soc Nephrol. 2020;31:1680-1682.
7. Blumenkrantz MJ, Kopple JD, Moran JK, et al. Nitrogen and urea metabolism during continuous ambulatory peritoneal dialysis. Kidney Int. 1981;20:78-82.
8. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395:1033-1034.
9. Pedersen SF, Ho YC. SARS-CoV2: a storm is raging. J Clin Invest. 2020;130:2202-2205.
10. Flores EA, Bastian BR, Pomposselli JJ, et al. Infusion of tumor necrosis factor/cachectin promotes muscle catabolism in the rat. A synergistic effect with interleukin 1. J Clin Invest. 1989;83:1614-1622.
11. Goodman MN. Interleukin-6 induces skeletal muscle protein breakdown in rats. Proc Soc Exp Biol Med. 1994;285:182-185.
12. Patel HJ, Patel BM. TNF-α and cancer cachexia: molecular insights and clinical implications. Life Sci. 2017;170:56-63.
13. Zhou J, Liu B, Laing C, et al. Cytokine signaling in skeletal muscle wasting. Trends Endocrinol Metab. 2016;27:335-347.
What is the extent of tissue catabolism in patients with COVID-19 associated acute kidney injury?

| Outcomes                      | Dietary Protein (g/day) | SUN (mg/dl) | Urea Nitrogen generation (UNA) (g/day) |
|-------------------------------|-------------------------|-------------|----------------------------------------|
| Acute peritoneal dialysis     | 74.8 ± 11               | 100.4 ± 33  | 10.2 ± 5                               |
| COVID-19 & AKI n=8            | p=0.51                  | p=0.11      | p=0.02                                 |
| Long-term ambulatory peritoneal dialysis | 67.2 ± 29               | 55.2 ± 12   | 4.7 ± 3                                |

**Conclusion:** In highly catabolic patients with COVID-19 and acute kidney injury, muscle protein breakdown seems to be the most likely explainable cause of endogenous source of urea generation, possibly due to cytokine storm.

Reference: Uribarri J, Sharma DE, Sharma S et al. Quantifying protein catabolic rate in a cohort of patients with COVID-19-associated AKI: a likely effect of the cytokine storm on muscle protein breakdown. Kidney Medicine. 2020.

Visual Abstract by Anja Yadav MD FASN

@docerluyedev