



Viewpoint

Carnitine deficiency in intensive care unit patients undergoing continuous renal replacement therapy—An underrecognized issue with potential for severe complications

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Introduction

Carnitine plays a crucial role in energy metabolism by transporting long-chain fatty acids into mitochondria for β -oxidation and removing waste metabolites.^[1] Approximately 98% of the body's total carnitine is stored in skeletal muscle, with blood serving as the transport medium.^[2] Carnitine is synthesized in the liver and kidneys from lysine and methionine, but endogenous production is limited. The body preserves carnitine levels through renal reabsorption and stores in organs such as skeletal muscles, the liver, kidneys, and heart.^[3] However, carnitine deficiency is prevalent in approximately 95% of hemodialysis patients due to extracorporeal loss during dialysis and impaired renal synthesis.^[4] L-carnitine replacement therapy can mitigate complications, including cardiac issues, anemia, and muscle weakness.^[5]

What Does Current Data Tell Us?

A recent retrospective single-center observational study assessed carnitine deficiency in intensive care unit (ICU) patients undergoing continuous renal replacement therapy (CRRT) from June 1, 2019, to March 31, 2020.^[6] The study included adults aged ≥ 20 years and measured carnitine levels in all CRRT patients during this period.^[6] Deficiency was defined as a free carnitine concentration $< 36 \mu\text{mol/L}$ or an acylcarnitine-to-free carnitine ratio exceeding 0.4, following Japanese Pediatric Society guidelines.^[7] Notably, carnitine deficiency was significantly

associated with sepsis, a recognized risk factor for carnitine depletion since its first documentation in 1989. This depletion is attributed to enzyme inhibition during the L-carnitine-mediated transport of long-chain fatty acids into mitochondria for β -oxidation.^[8] Carnitine, a small molecule with a molecular weight of 161 Da, decreases by 60%–70% after each hemodialysis session.^[9] In this study, 52.3% of CRRT patients exhibited carnitine deficiency, with higher dialysis flow rates correlating with greater depletion.^[9] Carnitine deficiency impairs fatty acid oxidation, leading to symptoms such as muscle weakness, rhabdomyolysis, cardiomyopathy, and arrhythmias.^[3] Furthermore, sepsis—a primary reason for initiating CRRT in the ICU—is a major contributor to ICU-acquired weakness.^[10] Alarmingly, 40% of patients who underwent CRRT experienced such severe muscle weakness that they struggled to stand upon ICU discharge.^[6]

Another study, a retrospective chart review at Duke University Hospital, examined serum micronutrient levels in ICU patients at high risk of malnutrition admitted between January 1, 2017, and December 31, 2018. The study analyzed levels of carnitine, copper, zinc, selenium, and vitamins B1, B6, B9, and C.^[11] The findings corroborated those of Oi et al.^[6] Among 106 ICU patients, 46% underwent CRRT, and 90% of these individuals had at least one micronutrient deficiency compared to 61% of non-CRRT patients ($P=0.002$). Copper ($P < 0.001$) and carnitine ($P < 0.001$) deficiencies were more prevalent in CRRT patients, while zinc deficiency was more common in non-CRRT patients ($P = 0.001$). The study emphasized the need for

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randomized controlled trials to define this emerging category of malnutrition and optimize supplementation strategies.^[11]

A recent case report underscores the clinical challenges of managing metabolic complications in critically ill patients. A 60-year-old man admitted with progressive respiratory failure due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) developed acute kidney injury (AKI) necessitating prolonged CRRT. Despite appropriate nutritional management, the patient experienced profound amyotrophy and significant weight loss, ultimately becoming unresponsive by day 85. A comprehensive metabolic evaluation revealed hyperammonemia, hypertriglyceridemia, and deficiencies in plasma free carnitine and copper. Remarkably, carnitine supplementation improved his neurological status and corrected the metabolic abnormalities. Van de Wyngaert et al.^[12] similarly reported a marked reduction in serum carnitine levels during hemodialysis, with 70%–80% of circulating carnitine eliminated in a single session. While muscle pools can initially compensate, prolonged hemodialysis exposure often leads to systemic carnitine deficiency, predisposing patients to heart failure, anemia, sarcopenia, and malnutrition, particularly in elderly individuals with end-stage kidney disease. These risks are frequently underestimated.^[12]

Are These Findings Applicable in Clinical Practice?

Routine monitoring of carnitine levels in ICU patients undergoing CRRT is recommended, with supplementation initiated when levels fall below the normal threshold of 20 $\mu\text{mol/L}$. Although formal guidelines are lacking, some authors propose an initial dose of 0.5–1 g/day.^[13] Certain medications, including pivampicillin, valproic acid, and verapamil, may exacerbate L-carnitine deficiency by inhibiting cellular transporters or increasing renal excretion. Extended artificial nutrition, typically devoid of L-carnitine, can further deplete endogenous stores. Since L-carnitine is generally stored in sufficient quantities, depletion often occurs only after more than 14 days of interrupted supply.^[13]

The mechanism linking reduced carnitine levels to higher sequential organ failure assessment (SOFA) scores remains unclear, though severe illness likely imposes significant metabolic stress on mitochondrial function.^[3] A randomized controlled trial investigating L-carnitine infusion in vasopressor-dependent septic shock demonstrated a reduction in 28-day mortality, suggesting potential benefits without reported adverse effects, although carnitine concentrations were not directly measured.^[14]

Monitoring the acylcarnitine-to-free carnitine (A/F) ratio may guide supplementation, as elevated acylcarnitine levels reflect impaired mitochondrial metabolism, reduced renal clearance, or disrupted carnitine transport. These imbalances can result in complications such as liver mitochondrial dysfunction.^[3,7] In hemodialysis patients, L-carnitine administration has been shown to redistribute acylcarnitine, enhancing its clearance and mitigating toxicity risks.^[12]

Conclusion

In the absence of robust data from randomized controlled trials specifically evaluating carnitine supplementation in CRRT patients, initiating supplementation when carnitine levels drop $<20 \mu\text{mol/L}$ is a prudent strategy. A starting dose of 0.5–1 g/day

may help prevent severe muscle weakness, hyperammonemia (in patients without liver dysfunction), and coma in mechanically ventilated individuals.

CRedit Authorship Contribution Statement

Arnaud Robert: Writing – review & editing, Writing – original draft, Conceptualization. **Julien Moury:** Writing – review & editing, Writing – original draft. **Gauthier Nendumba:** Writing – review & editing, Writing – original draft. **Benedicte Hauquier:** Writing – review & editing, Writing – original draft. **Ovidiu Vornicu:** Writing – review & editing, Writing – original draft. **Sydney Blackman:** Writing – review & editing, Writing – original draft. **Emily Perriens:** Writing – review & editing, Writing – original draft. **Nathan De Lissnyder:** Writing – review & editing, Writing – original draft. **Andriy Shchukin:** Writing – review & editing, Writing – original draft. **Farah El Yaakoubi:** Writing – review & editing, Writing – original draft. **Clara Saad:** Writing – review & editing, Writing – original draft. **Cyril Schmit:** Writing – review & editing, Writing – original draft. **Anne-Sophie Dincq:** Writing – review & editing, Writing – original draft. **Patrick Evrard:** Writing – review & editing, Writing – original draft. **Pierre Bulpa:** Writing – review & editing, Writing – original draft. **Isabelle Michaux:** Writing – review & editing, Writing – original draft. **Patrick M. Honore:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

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Ethics Statement

Not applicable.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

References

- [1] Hatamkhani S, Karimzadeh I, Elyasi S, Farsaie S, Khalili H. Carnitine and sepsis: a review of an old clinical dilemma. *J Pharm Sci* 2013;16(3):414–23. doi:10.18433/j3js4c.
- [2] Calò LA, Vertolli U, Davis PA, Savica V. L carnitine in hemodialysis patients. *Hemodial Int* 2012;16(3):428–34. doi:10.1111/j.1542-4758.2012.00679.x.
- [3] Bonafé L, Berger MM, Que YA, Mechanick JI. Carnitine deficiency in chronic critical illness. *Curr Opin Clin Nutr Metab Care* 2014;17(2):200–9. doi:10.1097/MCO.000000000000037.

- [4] Fornasini G, Evans AM. Analysis of free carnitine in the plasma of ESRD patients undergoing chronic dialysis: what is the best assay? *Dial Transplant* 2003;32(6):S2–12.
- [5] Higuchi T, Abe M, Yamazaki T, Okawa E, Ando H, Hotta S, et al. Levocarnitine improves cardiac function in hemodialysis patients with left ventricular hypertrophy: a randomized controlled trial. *Am J Kidney Dis* 2016;67(2):260–70. doi:10.1053/j.ajkd.2015.09.010.
- [6] Oi M, Maruhashi T, Asari Y. Carnitine deficiency in intensive care unit patients undergoing continuous renal replacement therapy: a single-center retrospective study. *JMA J* 2024;7(1):70–6. doi:10.31662/jmaj.2023-0112.
- [7] Japan Pediatric Society. Diagnostic and treatment guidelines for carnitine deficiency [Internet]. 2018 [cited 2023 Apr 30]. Available from: http://www.jpeds.or.jp/uploads/files/20181207_shishin.pdf. [Last accessed on 2024 June 12]
- [8] Eaton S, Fukumoto K, Stefanutti G, Spitz L, Zammit VA, Pierro A. Myocardial carnitine palmitoyltransferase I as a target for oxidative modification in inflammation and sepsis. *Biochem Soc Trans* 2003;31(6):1133–6. doi:10.1042/bst0311133.
- [9] Sgambat K, Moudgil A. Carnitine deficiency in children receiving continuous renal replacement therapy. *Hemodial Int* 2016;20(1):63–7. doi:10.1111/hdi.12341.
- [10] Zhou Y, Zhou F, Wang X, Chang P, Zhang L, Yao Q, et al. Practice of extracorporeal therapies for septic acute kidney injury patients in intensive care units in mainland China. *Blood Purif* 2019;47(Suppl 3):1–6. doi:10.1159/000499456.
- [11] Fah M, Van Althuis LE, Ohnuma T, Winthrop HM, Haines KL, Williams DGA, et al. Micronutrient deficiencies in critically ill patients receiving continuous renal replacement therapy. *Clin Nutr ESPEN* 2022;50:247–54. doi:10.1016/j.clnesp.2022.05.008.
- [12] Van de Wyngaert C, Dewulf JP, Collienne C, Laterre PF, Hantson P. Carnitine deficiency after long-term continuous renal replacement therapy. *Case Rep Crit Care* 2022;2022:4142539. doi:10.1155/2022/4142539.
- [13] Fukami K, Taguchi K. Carnitine deficiency in intensive care unit patients undergoing continuous renal replacement therapy. *JMA J* 2024;7(1):77–8. doi:10.31662/jmaj.2023-0200.
- [14] Oami T, Oshima T, Hattori N, Teratani A, Honda S, Yoshida T, et al. L-carnitine in critically ill patients – a case series study. *Ren Replace Ther* 2018;4:13. doi:10.1186/s41100-018-0158-7.