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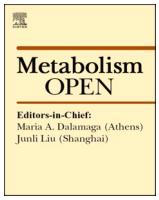

25-hydroxyvitamin D and parathyroid hormone in new onset sepsis: A prospective study in critically ill patients

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ABSTRACT

Hypovitaminosis D is highly prevalent in critically ill patients, and it has been suggested to be a risk factor for infections, sepsis and higher mortality. We sought to investigate whether serum 25-hydroxyvitamin D (25(OH)D) and parathyroid hormone (PTH) in critically ill patients with new onset sepsis are associated with severity and outcome. We prospectively included 50 consecutive critically ill adult cases with new onset sepsis and 50 healthy controls matched for age and sex. PTH and 25(OH)D were determined in serum via electrochemiluminescence immunoassays at inclusion in the study in all cases and controls, and one week after sepsis onset in cases. Patients had reduced 25(OH)D compared to controls at sepsis onset (7.9 ± 3 vs 24.6 ± 6.7 ng/mL, $p < 0.001$), whilst PTH was similar (median (range): 34.5 (5.7–218.5) vs 44.2 (14.2–98.1) pg/mL, $p = 0.35$). In patients, 25(OH)D upon enrollment and one week after did not differ significantly (7.9 ± 3 vs 7 ± 4.3 ng/mL, $p = 0.19$). All patients presented with hypovitaminosis D (25(OH)D < 20 ng/mL), while 40 patients (80 %) had vitamin D deficiency (25(OH)D < 12 ng/mL) at sepsis onset, including all ten (20 %) nonsurvivors, who died within 28 days from sepsis onset. Patients with sepsis (N = 28) and septic shock (N = 22) as well as survivors (N = 40) and non-survivors (N = 10) had similar 25(OH)D at enrollment ($p > 0.05$). 25(OH)D was positively correlated with ionized calcium ($r = 0.46$, $p < 0.001$) and negatively with PTH ($p < 0.05$), while inflammatory biomarkers or the severity scores exhibited no correlation with 25(OH)D. Patients with septic shock and nonsurvivors had lower PTH than patients with sepsis and survivors respectively (42.2 ± 42.9 vs 73.4 ± 61.9 pg/mL, $p = 0.04$, and 18.3 ± 10.7 vs 69.9 ± 58.8 pg/mL, $p = 0.001$, respectively). C-reactive protein was negatively associated with PTH ($r = -0.44$, $p = 0.001$). In conclusion, vitamin D deficiency was present in 80 % of critically ill patients at sepsis onset, while nonsurvivors exhibited lower PTH than survivors. Additional, larger and multicenter studies are warranted to elucidate the contribution of vitamin D and PTH to the pathogenesis of sepsis and its outcomes.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BMI, Body Mass Index; CRP, C-reactive protein; ECLIA, electrochemiluminescence immunoassay; ICU, Intensive Care Unit; IL, Interleukin; PTH, parathyroid hormone; SOFA, sequential organ failure assessment; VDR, Vitamin D Receptor; WBC, White Blood Cell; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D.

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1. Introduction

Vitamin D, a lipid-soluble hormone which modulates calcium homeostasis, exerts pleiotropic non-skeletal actions including glucose homeostasis, muscle function, cardiac contractility, mucosal barrier and endothelial function as well as immune modulation [1,2]. Vitamin D has several beneficial effects in multiple organs and systems by inhibiting inflammation and atherogenesis [2]. Hypovitaminosis D is strongly associated with obesity and its associated diseases such as metabolic syndrome, dyslipidemia, arterial hypertension and cardiovascular disorders [3–7]. Moreover, low vitamin D has been linked to susceptibility to infections, sepsis and a poor outcome [8,9].

Experimental studies in animal models and *ex vivo* human cells have demonstrated multiple biologic effects of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) -the active metabolite of vitamin D-on both the innate and adaptive immunity, promoting antibacterial response (pathogen recognition and clearance), and modulating inflammation, favoring an anti-inflammatory phenotype [10]. In particular, vitamin D stimulates macrophages, induces regulatory T cells and Th2 response, inhibits B lymphocyte proliferation and differentiation, modulates dendritic cell maturation and tumor necrosis factor expression, suppresses pro-inflammatory cytokines and induces the synthesis of anti-inflammatory cytokines [11,12]. Additionally, vitamin D promotes barrier function and production of antibacterial peptides and reactive oxygen species [13]. Clinical studies suggest that hypovitaminosis D is a risk factor for bacterial and viral respiratory infections and sepsis [14–17].

According to the most recent consensus statement, vitamin D deficiency is defined as 25-hydroxyvitamin D (25(OH)D) levels less than 12 ng/mL, 25(OH)D levels between 12 and 20 ng/mL define vitamin D insufficiency, while 25(OH)D levels between 20 and 50 ng/mL are considered safe and sufficient for skeletal health [18]. Vitamin D deficiency is highly prevalent in critically ill patients (in around 70 %), and it has been linked to poor outcomes [11,19–21]. Additionally, it is a risk factor for the development of severe infections and sepsis with worse clinical outcomes [8,9,16,21,22]. However, very few previous studies have investigated the alterations of the calcium-parathyroid hormone (PTH)-vitamin D axis in relation to sepsis in critically ill patients. We sought to investigate serum 25(OH)D and PTH in critically ill patients with new onset sepsis and their association with sepsis severity and outcome in a prospectively designed study.

2. Materials and methods

2.1. Study participants and design

We prospectively enrolled consecutive critically ill cases hospitalized in the Intensive Care Unit (ICU) of a tertiary academic hospital with new onset sepsis, fulfilling the SEPSIS-3 diagnostic criteria of sepsis or septic shock [23]. The protocol of the study has been published in the past [24–27]. Patients were enrolled within 48 h from sepsis diagnosis. All patients were ≥18 years of age. We also recruited healthy adults amid visitors of the outpatient Laboratory Department of the hospital, as controls matched for age (±5 years) and sex with the patients. We excluded from the study patients and controls with endocrine disease, chronic renal disease, malignancy, immunosuppression and vitamin D supplementation. Patients who stayed in the ICU for less than a week were excluded from the analysis. Demographic and clinical data as well as main laboratory data were recorded. We followed patients for 28 days from enrollment.

The Scientific and Ethics Committee of the hospital approved the study (#587/10-04-2013). The guidelines of the Declaration of Helsinki and its successive amendments were strictly followed. All subjects or their next of kin gave informed consent.

2.2. Laboratory analysis

Morning whole blood specimens were gathered from both cases and controls at inclusion in the study, with additional samples taken from patients one week after joining the study. All specimens were centrifuged to collect serum, which was kept at −80 °C for prospective analysis. Biochemical variables were measured using an automated analyzer (Roche Diagnostics Corporation, Indianapolis, Indiana, USA). Total 25 (OH)D and PTH (biologically intact PTH (1–84)) were determined in serum by electrochemiluminescence immunoassays (ECLIA) (Cobas, Roche Diagnostics Corporation, Indianapolis, Indiana, USA) upon enrollment, while 25(OH)D was also determined one week after enrollment.

2.3. Statistical analysis

Nominal parameters were assessed using the chi-square test. The normality hypothesis was tested with the Shapiro-Wilk test. For normally distributed continuous variables, the *t*-test and paired *t*-test were applied, whereas the Mann-Whitney *U* test and Wilcoxon matched-pair test were used for variables that were not normally distributed. Continuous variables were also analyzed using Spearman correlation coefficients (r) to determine the association between variables. P-values were two-sided, with a level of significance set at $\alpha = 0.05$. The statistical analysis was performed using IBM-SPSS® version 23 for Windows.

3. Results

Table 1 depicts clinical and laboratory variables in cases and controls. We included 50 critically ill cases with sepsis and 50 age- and gender-matched healthy controls. Twenty-eight patients (56 %) had sepsis and 22 patients (44 %) had septic shock at enrollment. Ten patients (20 %) died within 28 days from sepsis onset. Patients had similar BMI and phosphate levels compared to controls ($p = 0.052$ and $p = 0.3$ respectively); however, they had elevated white blood cell (WBC) count, serum creatinine and C-reactive protein (CRP), and lower thrombocytes and ionized calcium compared to controls ($p < 0.001$).

Patients with sepsis had significantly lower serum 25(OH)D than controls at sepsis onset (7.9 ± 3 vs. 24.6 ± 6.7 ng/ml, $p < 0.001$), but not PTH (median (range): 34.5 (5.7–218.5) vs. 44.2 (14.2–98.1) pg/mL,

Table 1
Clinical and laboratory parameters in cases (N = 50) and healthy controls (N = 50).

Variables	Cases (N = 50)	Controls (N = 50)	p-value
Age[a], in years	67.3 ± 11.4	70.8 ± 10.3	0.11
Sex, n (%)			
Male	28 (56)	28 (56)	
Female	22 (44)	22 (44)	1.00
BMI[a], kg/m^2	31.1 ± 6.9	28.8 ± 4.5	0.052
APACHE II score[a]	26.3 ± 8	–	–
SOFA score[a]	11 ± 3.5	–	–
Presence of septic shock, n (%)	22 (44)	–	–
Death before 28 day, n (%)	10 (20)	–	–
CRP[b], mg/L	130 (6.9–430)	3.3 (0.1–7.4)	<0.001
Procalcitonin[b], μg/L	0.9 (0.1–100)	–	–
White Blood Cells[a]/μL	14,402 ± 8918	7040 ± 1752	<0.001
Platelets[a] x 10^3/μL	182.9 ± 9	237.2 ± 3.9	<0.001
Creatinine[a], mg/dL	2.13 ± 2.5	0.85 ± 0.15	<0.001
Ionized Calcium[a], mg/dL	3.9 ± 0.4	4.7 ± 0.3	<0.001
Phosphate[a], mg/dL	3.3 ± 1.4	3.5 ± 0.5	0.3
PTH[b], pg/mL,	34.5 (5.7–218.5)	44.2 (14.2–98.1)	0.35
25(OH)D[a], ng/mL	7.9 ± 3	24.6 ± 6.7	<0.001

Abbreviations: APACHE II, acute physiology and chronic health evaluation; BMI, body mass index; CRP, C-reactive protein; PTH: parathyroid hormone; SOFA, sequential organ failure assessment; 25(OH)D: 25-hydroxyvitamin D.
[a] Mean ± SD.
[b] Median, range.

p = 0.35) (Fig. 1). Patients' serum 25(OH)D upon enrollment and one week after did not differ significantly (7.9 ± 3 vs. 7 ± 4.3 ng/mL, p = 0.19).

Hypovitaminosis D (serum 25(OH)D < 20 ng/mL) was detected in all patients at sepsis onset: 20 % had vitamin D insufficiency (12 ng/mL < 25(OH)D < 20 ng/mL) and 80 % had vitamin D deficiency (25(OH)D < 12 ng/mL). All ten patients who did not survive after 28 days had vitamin D deficiency upon enrollment. However, only 8 patients (16 %) presented an elevated PTH (>75 pg/ml), while 84 % had an impaired parathyroid response to low vitamin D (PTH ≤75 pg/ml).

Serum 25(OH)D levels were similar between patients with sepsis and septic shock as well as between survivors and nonsurvivors, at enrollment (p = 0.93 and p = 0.62 respectively) (Fig. 2 and Fig. 3). Patients with septic shock had significantly lower PTH than patients with sepsis (42.2 ± 42.9 vs 73.4 ± 61.9 pg/mL, p = 0.04), as well as nonsurvivors than survivors (18.3 ± 10.7 vs. 69.9 ± 58.8 pg/mL, p = 0.001) (Fig. 4).

Circulating 25(OH)D did not correlate with inflammatory parameters (WBC, CRP, procalcitonin) or the clinical severity measures (APACHE II, SOFA) in patients with sepsis (all p > 0.05), while it positively correlated with ionized calcium (r = 0.46, p < 0.001) and was inversely associated with PTH (r = −0.29, p = 0.03). PTH inversely correlated with CRP (r = −0.44, p = 0.001).

4. Discussion

In this prospectively designed study, we found that circulating 25(OH)D was significantly decreased in septic cases compared to healthy controls at the beginning of sepsis, while PTH did not differ significantly. We also showed that all septic cases had low circulating vitamin D: 20 % had vitamin D insufficiency, and 80 % of them, including all nonsurvivors, had vitamin D deficiency at enrollment. Finally, we found that PTH was significantly lower in cases with septic shock in comparison to those with sepsis, in nonsurvivors compared to survivors, and was inversely correlated with CRP.

Our findings are in accordance with previous data that demonstrate an increased prevalence of hypovitaminosis D in critically ill cases [11,19,20,28]. Evidence also suggests that decreased vitamin D is a risk factor for sepsis and a poor outcome [8,9,13,14,16,20]. A recent meta-analysis of 8 studies with 1736 cases showed that decreased 25(OH)D at admission was independently linked to an increased mortality in cases with sepsis [22]. Data from mechanistic, animal and human studies have shown that vitamin D deficiency may contribute to the susceptibility to a wide range of human diseases, including infections, inflammatory conditions, and neoplastic diseases [17,29–32]. Mendelian Randomization and observational studies have shown that circulating 25(OH)D below 25 nmol/L is linked to a higher risk of bacterial pneumonia [33]. Vitamin D may impact on the immune system. The majority of immune cells express the Vitamin D Receptor (VDR) and vitamin D metabolism–associated enzymes. More specifically, 1,25 $(OH)_2D$ may induce innate antimicrobial effector pathways such as the antibacterial proteins cathelicidin LL-37 and human beta-defensin 2 [34]. Furthermore, an important question is whether low vitamin D levels in sepsis could result from severe illness. During an acute phase reaction, serum levels of several vitamins are reduced [35]. Nevertheless, to date there are no data to support that vitamin D supplementation may improve sepsis outcomes [36].

In the current study, we failed to show any association of 25(OH)D with sepsis severity and death, possibly because we did not measure 1,25 $(OH)_2D$, which is the active metabolite expressing the physiologic

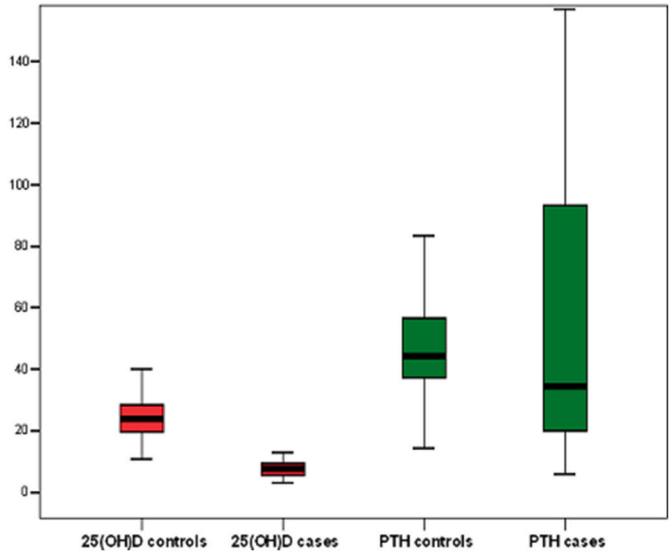

Fig. 1. Baseline circulating 25(OH)D (ng/ml) is lower in cases than controls (p < 0.001), while parathyroid hormone (PTH, pg/ml) do not differ significantly (p = 0.35).

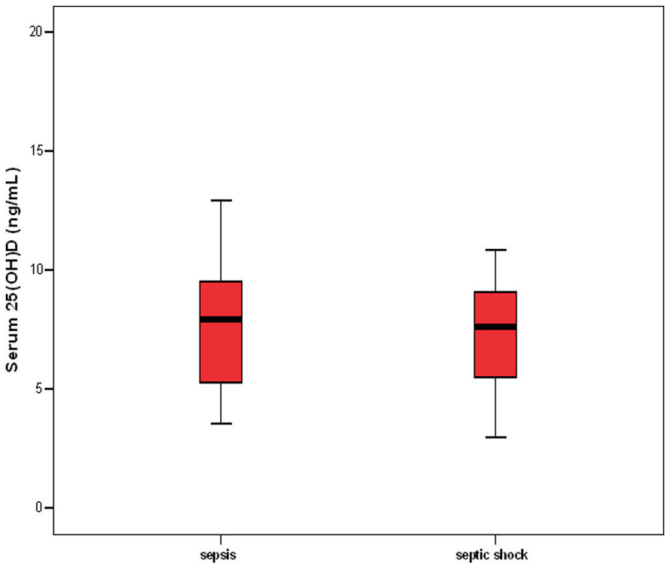

Fig. 2. Circulating 25(OH)D in patients with sepsis (N = 28) and septic shock (N = 22) at enrollment do not differ significantly (p = 0.93).

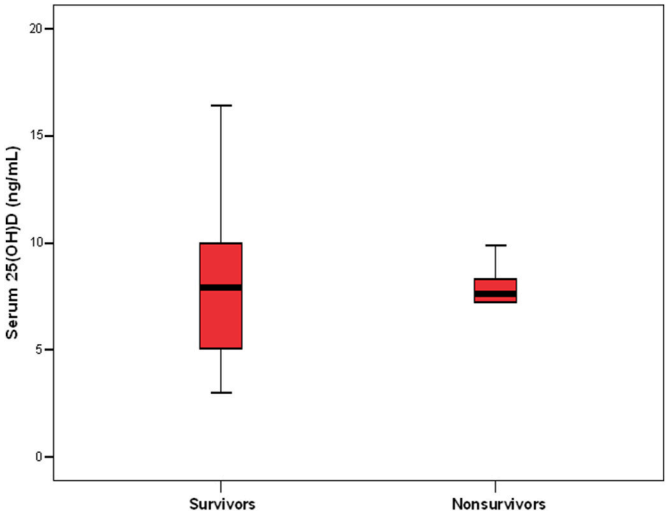

Fig. 3. Circulating 25(OH)D at enrollment in survivors (N = 40) and nonsurvivors (N = 10) do not differ significantly (p = 0.62).

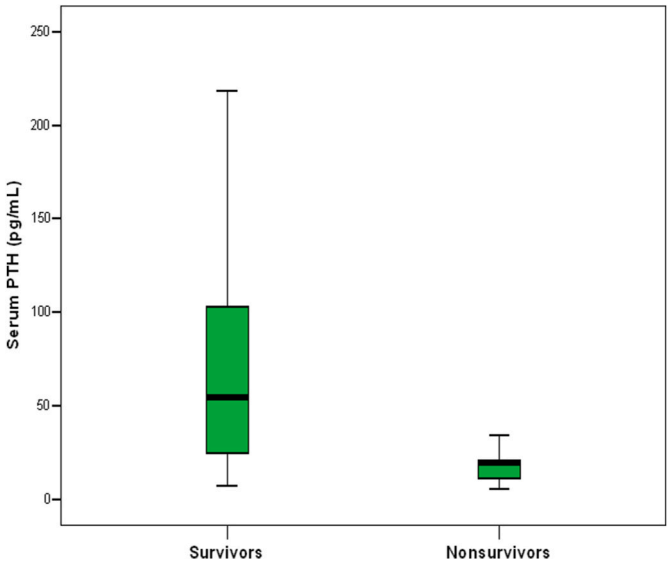

Fig. 4. Serum parathyroid hormone (PTH) at enrollment is significantly lower in nonsurvivors (N = 10) than survivors (N = 40) (18.3 ± 10.7 vs. 69.9 ± 58.8 pg/mL, p = 0.001).

actions of vitamin D. Indeed, circulating 25(OH)D levels are not generally associated with $1,25(OH)_2D$ levels [37]. A previous study in 91 cases with sepsis showed that $1,25(OH)_2D$ was significant lower in nonsurvivors compared to survivors, while 25(OH)D was not significantly different between these groups. Additionally, $1,25(OH)_2D$ was a significant predictor of 30-day mortality [38]. In a subsequent study, the same group of investigators found that increased PTH production could not overcome sepsis-associated $1,25(OH)_2D$ deficiency in septic humans and mice, whereas more complex mechanisms are involved [37].

We did not observe a significant difference in PTH between septic patients and controls. We also showed that 84 % of our patients presented a blunted parathyroid response to decreased circulating vitamin D. This result is in agreement with a recent study in critically ill children with sepsis [39]. However, studies in critically ill adults with or without sepsis have supported an elevated PTH, contrary to our findings [40–42]. In a pilot study of 37 critically ill patients, Carlstedt et al. found increased PTH that was associated with the severity and a poor outcome [41]. A prospective study in 100 critically ill patients demonstrated that hypovitaminosis D (<20 ng/ml) was highly prevalent (78 %) and persisted during ICU stay, while it was associated with the severity of disease. They also showed that 32.5 % of patients with low vitamin D presented secondary hyperparathyroidism, in contrast to our study [43]. Additionally, a prospective observational study in 216 critically ill cases hospitalized in a medical ICU showed that 44 % had 25(OH)D < 20 ng/ml and vitamin D deficiency was found to be an independent risk factor for 90-day mortality. Furthermore, cases with low vitamin D and secondary hyperparathyroidism (PTH >75 pg/ml) had higher mortality than those with decreased vitamin D and impaired parathyroid response (PTH ≤75 pg/ml), in contrast to our findings [44].

Very few studies have explored the parathyroid response specifically in patients with sepsis. In a prospective study of 48 critically ill cases with or without sepsis and 16 healthy controls, Greulich et al. found that septic patients had significantly lower 25(OH)D than non-septic patients and healthy controls, while PTH was higher in septic patients [45]. Czarnik et al. compared PTH in critically ill cases with renal failure undergoing continuous renal replacement therapies, with or without sepsis. They found higher PTH levels in septic patients [46]. The increased parathyroid response in sepsis may be due to increased catecholamines during sepsis that could act on β-adrenergic receptors on the parathyroid gland, stimulating PTH secretion. On the other hand, the parathyroid response during sepsis may be dissociated from vitamin D status, being influenced by the systemic inflammatory process [40]. Animal studies have shown that inflammatory molecules, such as interleukin-1 beta (IL-1β) and IL-6, may increase calcium-sensing receptors, decrease PTH levels, and induce hypocalcemia [47–49]. Moreover, it is important to emphasize that a single determination of PTH may not accurately represent the 24-h hormonal pattern and, consequently, might not reflect the underlying state in critically ill septic cases.

The strengths of our study lie in its prospective design and the meticulous selection of cases and controls based on predefined inclusion and exclusion criteria. However, the study has certain important limitations. The control group comprised healthy outpatients, and not critically ill cases without sepsis. Additionally, we did not have data on the levels of these hormones before the onset of sepsis. Therefore, we could not discriminate between the impact of critical illness and sepsis on 25(OH)D and PTH. The small sample size deterred further statistical analyses to demonstrate any significant associations of hypovitaminosis D with sepsis and its outcome. Also, we did not determine $1,25(OH)_2D$, the active metabolite of vitamin D, that exerts its physiologic actions. We did not use liquid chromatography–mass spectrometry for the determination of 25(OH)D which provides more accurate and consistent results; however, ECLIA methodology is a practical and widely used approach in hospital laboratory routine [34,50]. Finally, this is a single center study whereas its results may not be representative of other critically ill patients.

5. Conclusions

Critically ill cases with sepsis showed decreased vitamin D levels at sepsis onset. However, circulating 25(OH)D was not linked to sepsis severity and outcome. PTH was significantly lower in cases with septic shock and nonsurvivors in comparison to patients with sepsis and survivors. More prospective, multicentric and larger studies are required to unravel the contribution of vitamin D and parathyroid hormone to the pathogenesis of sepsis and its outcomes.

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Informed consent statement

Informed consent was obtained from all subjects involved in the study or their next of kin.

CRediT authorship contribution statement

Irene Karampela: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Theodora Stratigou:** Writing – review & editing, Methodology, Investigation. **Georgios Antonakos:** Formal analysis. **Dimitris Kounatidis:** Writing – review & editing, Investigation. **Natalia G. Vallianou:** Writing – review & editing, Investigation. **Dimitrios Tsilingiris:** Writing – review & editing, Investigation. **Maria Dalamaga:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare no conflict of interest.

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