

sions,² and we also did not detect aromatase protein in the glandular and stromal compartments of ectopic endometrial tissue. We recently found that what was believed to be aromatase protein was mainly endogenous biotin labeling or iron deposits.³ Using three different protocols, we found only barely detectable amounts of aromatase messenger RNA (mRNA). Among 21 peritoneal endometriotic lesions, 16 were aromatase-negative and 5 were near the limit of detection. Our results suggest that aromatase produced within endometriotic lesions might not be as important in endometriosis as postulated in Bulun's review.

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THE AUTHOR REPLIES: Biologically relevant levels of aromatase and its product estradiol in vertebrate tissues are lower by a factor of 100 to 100,000 than the levels of most other steroidogenic proteins and their products. Thus, the accurate evaluation of aromatase expression and enzyme levels in extraglandular cells and tissues is a complex task and requires a laboratory with substantial expertise and experience in making such

measurements. Since the mid-1990s, several laboratories in various parts of the world have consistently reported aromatase mRNA and enzyme activity in endometriotic tissues and cells.¹⁻⁴ My colleagues and I have reported the presence of aromatase in endometriosis, and we have described the signaling pathway responsible for coordinated induction of aromatase and other steroidogenic genes required for the production of estradiol from cholesterol in endometriotic tissue.¹ The letter by Colette and Donnez contradicts their recently published article in which they reported that aromatase mRNA was detected in all but 2 of the approximately 60 samples of ovarian, peritoneal, and deep endometriotic tissues they studied.⁵

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Vitamin D Deficiency in Critically Ill Patients

TO THE EDITOR: Vitamin D deficiency is rarely considered or treated in critically ill patients. However, we recently reported three cases of life-threatening hypocalcemia secondary to vitamin D deficiency,^{1,2} highlighting potential acute complications. The prevalence of vitamin D deficiency and its significance in the intensive care unit (ICU) are unknown.

We performed a prospective study of the vitamin D status in ICU patients (Table 1) referred to the Department of Endocrinology, St. Vincent's

Hospital, Sydney, between January 2007 and January 2008. Demographic, physiological, and biochemical variables were recorded, including the Simplified Acute Physiology Score II (SAPS II) (on a scale of 0 to 163, with higher scores indicating more severe organ dysfunction).³

Among approximately 1100 ICU patients per year, the mean (\pm SD) serum level of 25-hydroxyvitamin D in 42 referred patients was 41 ± 22 nmol per liter (16 ± 9 ng per milliliter), with a high prevalence of hypovitaminosis D (Table 1). Moreover,

three patients died (from metastatic thymic carcinoma, glioma, and lymphoma), and all patients who died had undetectable levels of 25-hydroxyvitamin D. The SAPS II in patients with sufficient, insufficient, and deficient levels of vitamin D were 34 ± 11 , 45 ± 13 , and 51 ± 13 , with predicted mortality rates of 16%, 35%, and 45%, respectively.³

The level of 25-hydroxyvitamin D correlated with the level of ionized calcium ($r=0.78$, $P<0.01$) and the SAPS II ($r=-0.52$, $P<0.01$) but not with the level of serum albumin. The SAPS II also correlated with the level of ionized calcium ($r=-0.36$, $P=0.02$), but the only independent predictors of the SAPS II were the level of 25-hydroxyvitamin D ($\beta=-0.59$, $P<0.001$) and age ($\beta=0.33$, $P<0.02$). The level of serum creatinine and use or nonuse of corticosteroids and calcium or vitamin D supplements were not predictors of the SAPS II.

The current study involving patients in the ICU reveals a high prevalence of hypovitaminosis D that was associated with adverse outcomes, independently of hypocalcemia and hypoalbuminemia. Supplementation with calcium (at a mean dose of 645 ± 307 mg per day), vitamin D (at a mean dose of 820 ± 280 IU per day), or both before admission was not protective.

The cause of hypovitaminosis D is probably multifactorial. Although limited exposure to sunlight during chronic illness is probably an important factor, altered vitamin D and parathyroid metabolism during critical illness cannot be ruled out.

Vitamin D deficiency is associated with increased mortality.⁴ This study cannot establish causality between hypovitaminosis D and adverse outcomes. However, vitamin D has pleiotropic effects in immunity, endothelial and mucosal functions, and glucose and calcium metabolism. The association between hypovitaminosis D and common conditions (e.g., the systemic inflammatory response syndrome, septicemia, and cardiac and metabolic dysfunctions) in critically ill patients may be important. Vitamin D–deficient and vitamin D–insufficient states may worsen existing immune and metabolic dysfunctions in critically ill patients, leading to worse outcomes.

A total of 17% of the ICU patients in our study had undetectable levels of vitamin D. Referral bias may have led to the selection of a cohort of patients with worse vitamin D status, as compared with unreferred patients, but hypocalcemia was identified as a reason for referral in only 5% of

Table 1. Characteristics of 42 Critically Ill Patients Referred for Endocrinologic Evaluation.

Characteristic	No. of Patients (%)
Sex	
Male	20 (48)
Female	22 (52)
Diagnosis	
Cardiac disease	3 (7)
Neurologic disease	3 (7)
Metabolic disease	3 (7)
Trauma	5 (12)
Sepsis	13 (31)
Respiratory disease	15 (36)
Condition identified as reason for referral*	
Hyperglycemia	27 (64)
Abnormal thyroid function	15 (36)
Hyponatremia	12 (29)
Hypocortisolemia	8 (19)
Hypocalcemia	2 (5)†
Medications	
Corticosteroids	28 (67)
Calcium supplement	12 (29)
Vitamin D supplement	10 (24)
Level of 25-hydroxyvitamin D	
Sufficient, >60 nmol/liter	3 (7)
Insufficient, >30 to ≤60 nmol/liter	23 (55)
Deficient, >15 to ≤30 nmol/liter	16 (38)
Undetectable, ≤15 nmol/liter	7 (17)

* Referrals could specify more than one condition.

† Only one of the two patients had an undetectable level of 25-hydroxyvitamin D.

the patients. These findings highlight the need for consideration of vitamin D status and supplementation in patients in the ICU.

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Dr. Eisman reports receiving consulting fees from Amgen, deCODE Genetics, Eli Lilly, GE Lunar, Merck Sharpe & Dohme, Novartis, Roche–GlaxoSmithKline, Sanofi-Aventis, Servier, and Wyeth Australia and grant support from Novartis, Merck, and Sanofi-Aventis; and Dr. Center, lecture fees from Eli Lilly and Sanofi-Aventis. No other potential conflict of interest relevant to this letter was reported.

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