

Assessment of Calcium Homeostasis in the Critically Ill Surgical Patient

The Diagnostic Pitfalls of the McLean-Hastings Nomogram

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Hypocalcemia is a common problem in critically ill surgical patients. We prospectively evaluated whether measurement of the total serum calcium (Ca) concentration or calculation of the serum ionized Ca level (by the McLean-Hastings nomogram) accurately reflects the measured serum ionized Ca level. Although 71% and 58% of 156 predominately surgical intensive care unit (ICU) patients were hypocalcemic by the total serum Ca or calculated ionized Ca level, respectively, only 12% were hypocalcemic by directly measured serum ionized Ca measurement. The total serum Ca and calculated ionized Ca concentrations were sensitive (95% and 89%, respectively) but lacked specificity (32% and 46%, respectively) in predicting ionized hypocalcemia. Analyses of Ca binding to albumin in the serum of surgical ICU patients and normal subjects suggested that there is a circulating factor in critically ill patients that increases the binding of Ca to albumin. These observations may explain why the McLean-Hastings nomogram underestimates the protein-induced changes in serum Ca in critically ill surgical subjects. We conclude that: (1) total serum Ca and calculated ionized Ca concentrations are poor indicators of the true serum ionized Ca status in critically ill surgical patients, and we recommend direct measurement of serum ionized Ca levels in these patients; and (2) variability in the affinity of Ca for binding proteins in critical illness may explain the poor correlation between serum total and ionized Ca measurements.

THE TOTAL SERUM CALCIUM (Ca) is divisible into three fractions: a protein bound fraction, a diffusible but nonionized chelated fraction, and an ionized fraction. Although most hospital laboratories measure only the total

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serum Ca concentration, it is the ionized fraction that is physiologically active and homeostatically regulated. Alterations in the circulating ionized Ca concentration may effect cardiac, respiratory, and neuromuscular function and should therefore be closely monitored in critically ill patients.¹ In a previously reported retrospective analysis of 210 intensive care unit (ICU) patients, we found 64% to have below normal total serum Ca levels.² Since abnormalities in serum protein and arterial pH (each of which alters ionized Ca) are common in critically ill patients,² and because calculated ionized Ca levels may not adequately reflect the true serum ionized Ca value,^{3,4} we prospectively evaluated the ability of the total serum Ca concentration (with and without correction for serum albumin, protein, and arterial pH) to predict the measured serum ionized Ca level in 156 critically ill patients. Our findings in these initial studies prompted us to perform two further analyses to explain our results. All three experiments appear in this report.

Methods

Experiment A

One hundred and fifty-six predominantly surgical (approximately 80% surgical, 20% medical) ICU patients were prospectively studied in a protocol approved by our hospital's Clinical Investigation and Protection of Human Subjects Committees. The patients' clinical histories, diagnoses, and prescribed medications were recorded. On

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TABLE 1. Serum Calcium (Ca), Protein, and Arterial pH Values from 156 Critically Ill Patients

	Patients Mean ± SEM (Range)	Range of Normal Values
Total serum		
Ca (mg/dl)	8.06 ± 0.07 (6.1–12.2)	8.5–10.5
Calculated ionized		
Ca (mg/dl)	3.99 ± 0.04 (3.0–5.6)	4.1–5.1
Albumin (g/dl)	3.10 ± 0.5 (1.8–4.7)	3.5–5.0
Total protein (g/dl)	5.60 ± 0.08 (3.8–8.1)	6.0–8.4
Arterial pH	7.42 ± 0.004 (7.25–7.53)	7.35–7.45
Measured ionized		
Ca (mg/dl)	4.51 ± 0.04 (2.5–6.8)	4.1–5.1

admission to the ICU (and in the fasting state), blood samples were collected for measurement of serum Ca, albumin, total protein, phosphorus, creatinine, magnesium (Mg), urea nitrogen, ionized Ca, and arterial pH. Total serum Ca, albumin, protein, phosphorus, urea nitrogen, and creatinine levels were measured by a Technicon SMA II autoanalyzer (Technicon Corp., Tarrytown, NY). Serum Mg levels (normal range: 1.4–2.6 mg/dl) were measured by atomic absorption spectrometry, and the arterial pH was determined using a Corning 175 blood gas analyzer (Corning, Medfield, MA). The serum ionized Ca concentration (normal range: 4.1–5.1 mg/dl) was determined in duplicate by using an ion selective electrode (Nova 2, Nova Biomedical, Newton, MA). Blood samples for measurement of ionized Ca were collected anaerobically in red top vacutainer tubes, allowed to clot, and then the serum was separated anaerobically from cells by centrifugation at body temperature. In addition to measuring ionized Ca, we also calculated ionized Ca by use of the McLean-Hastings nomogram.⁵ Patients were classified as being hypocalcemic if the total serum Ca was <8.5 mg/dl, calculated ionized Ca was <4.1 mg/dl, or the measured ionized Ca level was <4.1 mg/dl. They were classified as hypercalcemic if the total serum Ca was >10.5 mg/dl, the calculated ionized Ca was >5.1 mg/dl, or the measured ionized Ca was >5.1 mg/dl.

Heart rate was recorded on all patients. When patients had in-dwelling arterial and Swan-Ganz catheters, mean arterial blood pressure (MAP) and cardiac output (by thermodilution) were also recorded at the time of blood collection.

The serum ionized Ca, total serum Ca, and per cent serum ionized Ca were determined in 145 fasting outpatients and compared to those of the critically ill patients.

Experiment B

Total serum Ca and albumin levels were serially monitored in 13 initially hypoalbuminemic, critically ill surgical patients who were given parenteral nutrition during their stay in the ICU. A regression line for a plot of calcium

versus albumin concentrations was drawn for each patient by the method of least squares.

Experiment C

Serum was obtained from six critically ill postoperative patients (3 with ionized hypocalcemia and 3 with ionized eucalcemia) and six age- and sex-matched normal subjects. The changes in the measured serum ionized Ca level and the per cent ionized Ca following the addition of Ca-free albumin (12.5 mg, 25 mg, 125 mg) to 1.5 ml of the six patient and six control sera were measured.

The equilibrium constant (K_{Ca}) in L/mole for Ca binding to protein in serum from the six critically ill and six well patients was calculated according to the method of Pedersen⁶:

$$K_{Ca} = \frac{CaPr}{(Cai) \times (mTPr - CaPr)}$$

where CaPr is protein-bound Ca in mol/L, Cai is ionized Ca in mol/L, m is the conversion factor (0.12 mmol Ca/g protein) for conversion of total protein (TPr) concentration in g/L to moles of Ca-binding sites/L, calculated from Scatchard analysis. CaPr was estimated as the difference between total serum Ca and ionized Ca. Since both groups of patients had similar serum concentrations of bicarbonate and phosphate, were not receiving blood transfusions (e.g., citrate), had no renal or hepatic disease, and were not hypothermic, this approximation of CaPr was felt to be valid.

Statistical Methods

Data are presented as the mean ± SEM and were analyzed by scatter diagrams, Chi square analysis, and Pearson's product correlation coefficients. Per cent sensitivity, specificity, false-negatives, false-positives, predictive value of a negative test, and predictive value of a positive test⁷ for total serum and calculated ionized Ca concentrations were calculated by using the measured serum ionized Ca level as the true measure of Ca status (TP = true-positives, TN = true-negatives, FP = false positives, FN = false-negatives):

% sensitivity = per cent of patients with hypo- or hypercalcemia detected by tests = $(TP/(TP + FN)) \times 100$

% false negatives = per cent of patients with hypo- or hypercalcemia not detected by tests = $(FN/(TP + FN)) \times 100$

% specificity = per cent of patients not hypo- or hypercalcemic who were correctly labeled by the tests = $(TN/(TN + FP)) \times 100$

% false-positives = per cent of patients not hypo- or hypercalcemic who were incorrectly labeled by the tests = $(FP/(TN + FP)) \times 100$

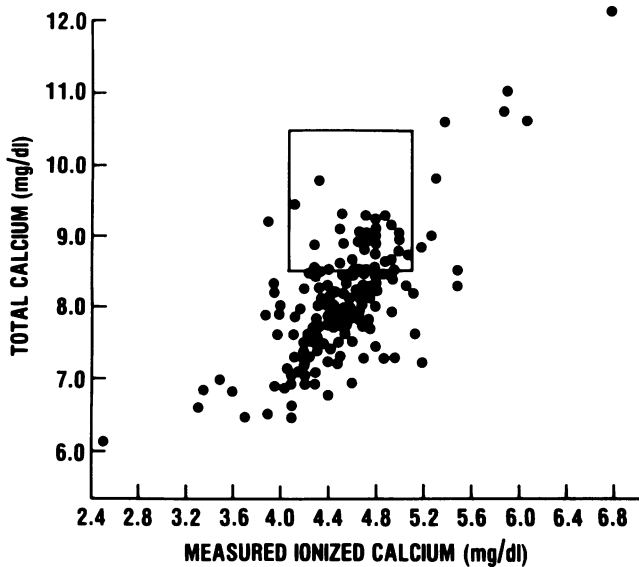


FIG. 1. Total serum calcium vs. measured serum ionized calcium levels. The boxed area marks the normal levels for both measurements. Note that although there is a linear correlation between the two variables ($r = 0.63$, $p < 0.05$), many total serum calcium values that are below normal are within the normal ionized calcium range.

Predictive value of a negative test (%) = Probability that hypo- or hypercalcemia is *not* present when the test is negative = $(TN/(TN + FN)) \times 100$

Predictive value of a positive test (%) = Probability that hypo- or hypercalcemia *is* present when the test is positive = $(TN/(TP + FP)) \times 100$

Results

Experiment A

The mean total serum Ca, calculated ionized Ca, albumin, and total protein values in the critically ill patients were less than the lower limit of normal (Table 1). By contrast, the patients' mean measured serum ionized Ca level and arterial pH were within the normal range. Both total serum Ca (Fig. 1) and calculated ionized Ca levels (Fig. 2) correlated ($p < 0.05$ for both; $r = 0.63$ and 0.45 , respectively) with the measured serum ionized Ca values. Despite these correlations, many abnormally low total Ca and calculated ionized Ca values were within the normal range of measured serum ionized Ca (Figs. 1 and 2).

The total serum Ca and calculated ionized Ca concentrations failed adequately to detect true, measured ionized hypocalcemia and hypercalcemia (Tables 2 and 3). Total serum Ca had a 95% sensitivity but only a 32% specificity for detecting measured ionized hypocalcemia (Table 3). The total serum Ca had a 100% specificity for detecting hypercalcemia but lacked sensitivity (38%). Calculated ionized Ca had poor sensitivity (89%) and specificity (46%) for detecting ionized hypocalcemia; its sensitivity

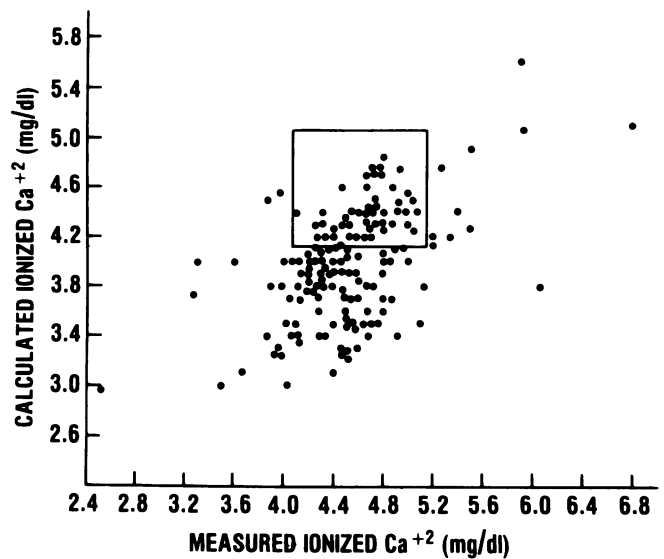


FIG. 2. Calculated serum ionized calcium (McLean-Hastings nomogram) vs. measured serum ionized calcium levels. The boxed area marks the normal levels for both measurements. Note that although there is a linear correlation between the two variables ($r = 0.45$, $p < 0.05$), many calculated ionized calcium values that are below normal are within the normal measured ionized calcium range.

for detecting hypercalcemia was extremely low (15%) but its specificity was high (100%). Thus, both methods (total serum Ca and calculated ionized Ca) were strongly suggestive of hypercalcemia when elevated (predictive values of positive tests = 100%) but poor for predicting hypocalcemia when decreased (predictive value of positive test = 16% and 6%, respectively) (Table 3). Similar results for the usefulness of calculated ionized Ca were obtained when ionized Ca concentrations were calculated by the method of Moore,⁸ which adjusts the serum Ca for changes in arterial pH and serum protein levels.

Patients were divided into three groups based on their measured serum ionized Ca levels (Table 4). Patients in the three groups were of similar age. The male:female ratio was higher in the eucalcemic patients than in either the hypercalcemic or hypocalcemic patients. Patients with sepsis and malignancy were more likely to be hypocalcemic, while patients with hepatic encephalopathy were more likely to be either hyper- or hypocalcemic than eu-

TABLE 2. Numbers of Patients with High, Low, or Normal Serum Calcium (Ca) Values

	Low (%)	Normal (%)	High (%)
Total serum Ca (mg/dl)	111/156 (71%)*	40/156 (26%)*	5/156 (3%)
Measured ionized Ca (mg/dl)	19/156 (12%)	124/156 (80%)	13/156 (8%)
Calculated ionized Ca (mg/dl)	91/156 (58%)*	63/156 (41%)*	2/156 (1%)*

* $p < 0.05$ compared to measured ionized Ca.

TABLE 3. Sensitivities and Specificities for Total Serum Calcium (Ca_t) and Calculated Ionized Calcium (Ca_c) in the Detection of True Measured Ionized Hypocalcemia and Hypercalcemia

	Hypocalcemia*		Hypercalcemia*	
	Ca_t	Ca_c	Ca_t	Ca_c
% Sensitivity	95%	89%	38%	15%
% False-negatives	5%	11%	62%	85%
% Specificity	32%	46%	100%	100%
% False-positives	68%	54%	0%	0%
Predictive value of negative test (%)	98%	97%	95%	93%
Predictive value of positive test (%)	16%	6%	100%	100%

* Refers to true, measured ionized hypocalcemia and hypercalcemia.

calcemic (Table 4). (The N for these subgroups is small, therefore the statistical significance may be misleading). Of the seven hypocalcemic patients with malignancy, five were hypomagnesemic, and two had sepsis.

The hypocalcemic patients had significantly ($p < 0.05$) lower serum Mg levels and higher serum urea nitrogen and creatinine levels than the eucalcemic patients (Table 5). Fifty-three per cent (10 of 19) of the hypocalcemic patients had an abnormal serum Mg level. Despite these observations, we found no correlation between the serum Mg level and the total serum Ca, ionized Ca, or per cent

TABLE 4. Clinical Diagnoses in Hypocalcemic, Eucalcemic, and Hypercalcemic Patients

	Hypocalcemic (N = 19)	Eucalcemic (N = 124)	Hypercalcemic (N = 13)
Ionized Ca (mg/dl)	<4.1	4.1-5.1	>5.1
Mean age (years)	53 ± 4	56 ± 2	53 ± 4
Females	9 (47%)*	30 (23%)	4 (31%)
Males	10 (53%)*	96 (77%)	7 (54%)
Cardiac surgery†	2 (11%)	24 (19%)	3 (23%)
Abdominal surgery†	2 (11%)	11 (9%)	1 (8%)
Malignancy	7 (37%)*	8 (6%)	2 (15%)
Head and neck surgery†	1 (5%)	6 (5%)	2 (15%)
Sepsis	5 (26%)*	4 (3%)	1 (8%)
ARDS	1 (5%)	5 (4%)	2 (15%)
Neurosurgery†	0 (0%)*	7 (6%)	0 (0%)*
GI bleed	4 (21%)	7 (6%)	0 (0%)*
Hepatic encephalopathy	2 (11%)*	0 (0%)	3 (23%)*
Other‡	2 (11%)	60 (48%)	2 (15%)
Died	3 (16%)	6 (6%)	1 (8%)

* $p < 0.05$ compared to eucalcemic group. Note that the N in some of these subgroups is small; therefore, the reader is cautioned that the statistical significance may have limited importance.

† These patients were in the ICU for 72 hours or less after their operation. All required postoperative mechanical ventilatory support.

‡ Many of the patients in this group had postoperative complications such as respiratory failure (>72 hours postoperative), hypotension, or bowel obstruction.

TABLE 5. Biochemical Parameters

	Hypocalcemic (N = 19)	Eucalcemic (N = 124)	Hypercalcemic (N = 13)
Ionized Ca (mg/dl)	<4.1	4.1-5.1	5.1
Serum Mg >2.6 mg/dl	3 (16%)	0 (0%)	1 (8%)
<1.4 mg/dl	7 (37%)*	18 (14%)	1 (8%)
<1.0 mg/dl	4 (21%)*	0 (0%)	0 (0%)
Serum PO_4 >4.5 mg/dl	3 (16%)	6 (5%)	0 (0%)
<2.0 mg/dl	1 (5%)	12 (10%)	1 (8%)
BUN† >25 mg/dl	7 (37%)*	5 (4%)	3 (23%)*
Creatinine >2.0 mg/dl	2 (11%)*	4 (3%)	1 (8%)

* $p < 0.05$ compared to eucalcemic group

† BUN = blood urea nitrogen.

ionized Ca values in the total group of critically ill patients. The serum phosphorus level tended ($0.05 < p < 0.1$) to be higher in the hypocalcemic group, although statistical significance was not achieved.

Mg abnormalities, sepsis, and malignancy were the most common states associated with hypocalcemia, whereas hepatic encephalopathy, malignancy, and hyperparathyroidism most commonly accompanied hypercalcemia (Table 6). Aminoglycosides and cimetidine were used more often in hypocalcemic than eucalcemic patients, while intravenous Ca, terbutaline, and narcotics were used more frequently in hypercalcemic patients. There was no relationship between hypocalcemia and blood transfusion for the groups as a whole; however, ionized hypocalcemia (3.9 mg/dl) did develop in one patient (with normal renal and hepatic function) who received rapid (1.5 ml/kg/min) blood transfusion therapy for gastrointestinal hemorrhage. We found no relationship be-

TABLE 6. Conditions Associated with Abnormal Calcium Status

Hypocalcemia (N = 19)†	Hypercalcemia (N = 13)‡
Magnesium abnormality (N = 10)	Hepatic encephalopathy (N = 3)
Sepsis (N = 5)	Malignancy (N = 2)
Malignancy (N = 7)*	Hyperparathyroidism (N = 2)
Hyperphosphatemia (N = 3)	Drugs
Renal failure (N = 2)	Calcium (N = 5)
Hepatic Encephalopathy (N = 2)	Narcotics (N = 7)
Rapid Blood Transfusion (N = 1)	Terbutaline (N = 4)
Drugs	
Aminoglycosides (N = 9)	
Cimetidine (N = 10)	

* Hypomagnesemia occurred in five of the seven patients and sepsis in the remaining two patients.

† Of the 19 hypocalcemic patients, 15 were surgical and four were medical patients.

‡ Of the 13 hypercalcemic patients, eight were surgical and five were medical patients.

TABLE 7. Hemodynamic Variables

	Hypocalcemic	Eucalcemic	Hypercalcemic
Ionized Ca (mg/dl)	<4.1	4.1-5.1	>5.1
Heart rate (beats/min)	103 ± 4	96 ± 2	102 ± 5
Mean arterial pressure (mmHg)	82 ± 4 (N = 14)	88 ± 2 (N = 78)	86 ± 3 (N = 13)
Cardiac output (L/min)	7.1 ± 0.9 (N = 7)	6.0 ± 0.3 (N = 35)	7.6 ± 0.8 (N = 3)

tween either the length of ICU stay (or mortality) and the measured serum ionized Ca concentration.

Heart rate, MAP, and cardiac output were similar in all groups of patients (Table 7, Figs. 3A and 3B). Serum Ca concentrations returned to normal levels with institution of Ca replacement therapy in all patients.

Measured serum ionized Ca levels were similar in the 156 critically ill patients and 145 well outpatients (4.51 ± 0.04 vs. 4.54 ± 0.1 mg/dl); however, the per cent ionized Ca was significantly ($p < 0.001$) higher in the critically ill compared to the well patients (56.3 ± 0.04 vs. $47.4 \pm 0.13\%$, respectively). The per cent ionized Ca varied from 42 to 67% in the 156 critically ill patients and was inversely correlated ($r = -0.6$, $p < 0.05$) with the total serum Ca concentration (Fig. 4).

Experiment B

Thirteen patients with low serum albumin concentrations were monitored over 2-3 week periods in the ICU while receiving parenteral nutrition, which raised their serum albumin levels. Total serum Ca was serially measured as the serum albumin levels increased. The rise in Ca for a given rise in albumin varied greatly among patients (Fig. 5).

Experiment C

We analyzed the serum from six critically ill patients and six normal individuals for the presence of factors that

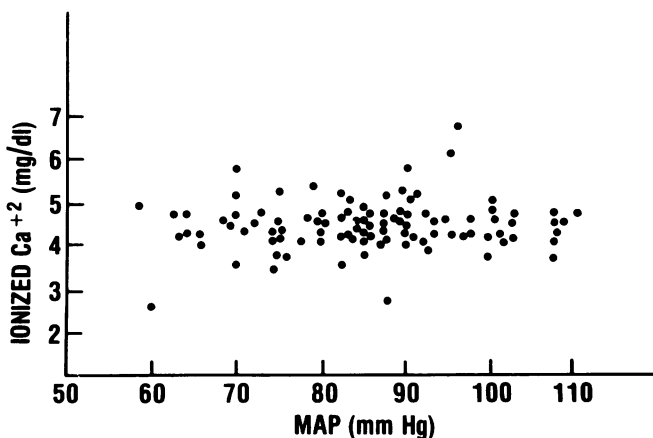


FIG. 3A. Measured serum ionized calcium vs. mean arterial blood pressure (MAP). The observed scattergram reflects a lack of correlation.

alter Ca binding to serum proteins by studying the *in vitro* effect of the addition of various amounts of Ca-free albumin on the serum ionized Ca and per cent ionized Ca levels. Increasing amounts of albumin caused a progressive decrease in ionized Ca and per cent ionized Ca (Fig. 6), attributable to albumin binding of free Ca. Sera from patients with critical illness caused a much greater decrease in ionized Ca and per cent ionized Ca, suggesting the presence of a factor in the serum that increased Ca binding to albumin. All six critically ill patients had a greater decrease in ionized Ca and per cent ionized Ca when compared to the normal individuals. The K_{Ca} for protein binding of Ca was calculated in six critically ill and six healthy subjects and was found to be significantly ($p < 0.01$) elevated in the critically ill patients (191 ± 12.2 vs. 139 ± 6.8 L/mol) compared to the normal controls.

Discussion

Abnormally low total serum Ca and calculated ionized Ca levels are common in critically ill patients.² As in our retrospective study,² we have now prospectively found that greater than 50% of critically ill patients have low total serum Ca and calculated ionized Ca values by either the McLean-Hastings nomogram or by the method of Moore.⁸ In agreement with our findings, Fenton et al.⁹ recently described a discordance between serum total and measured ionized Ca levels in patients with thermal burns. Szyfebein and coworkers¹⁰ also studied Ca homeostasis in 25 patients following thermal injury and found poor correlations between the serum total Ca or calculated (McLean-Hastings nomogram) ionized Ca levels and directly measured serum ionized Ca values. Other studies^{8,11-14} have demonstrated equally poor correlations

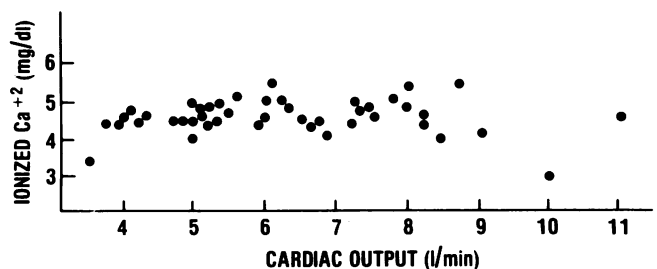


FIG. 3B. Measured serum ionized calcium vs. cardiac output. The observed scattergram reflects a lack of correlation.

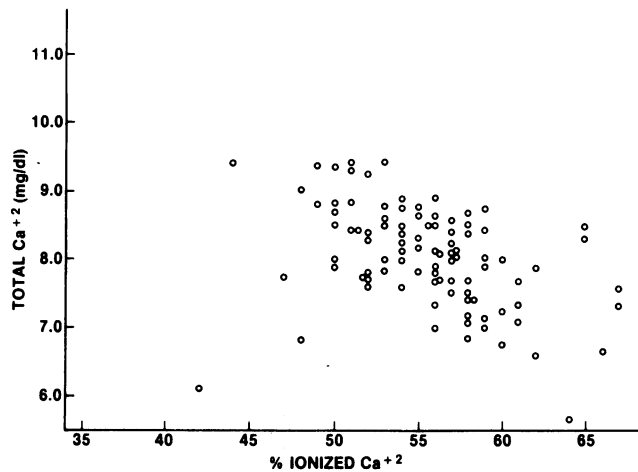


FIG. 4. Total serum calcium vs. the per cent ionized calcium. An inverse relationship between the two variables exists ($r = 0.60$, $p < 0.05$).

between the serum total Ca levels and measured serum ionized Ca concentrations. Even when the total serum Ca is corrected for circulating protein levels and arterial pH, the correlations remained poor.^{11,12,14}

Our study shows that critically ill patients with low serum total Ca and calculated ionized Ca levels infrequently have (measured) ionized hypocalcemia (32% specificity). On the other hand, the presence of a normal total serum and/or calculated ionized Ca level is good evidence against ionized hypocalcemia (predictive value of a negative test = 98%). Serum total Ca and calculated ionized Ca values failed to detect most ionized hypercalcemic patients (sensitivity 38% and 15%, respectively);

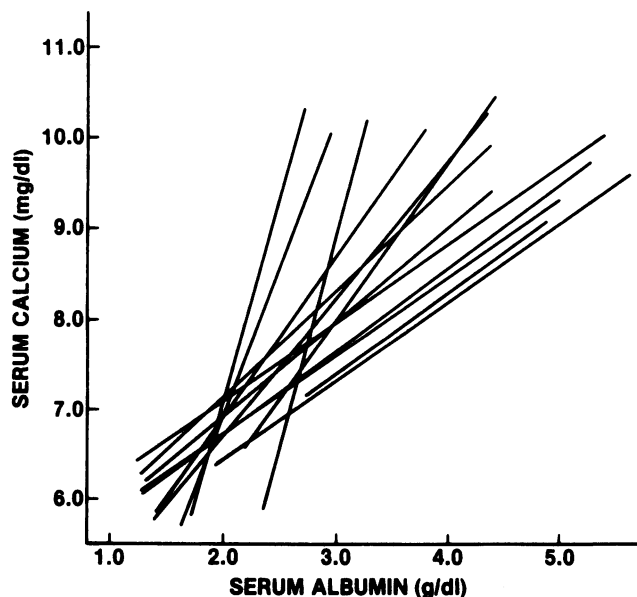


FIG. 5. Total serum calcium vs. serum albumin levels in 13 critically ill patients followed over 2-3 weeks. The slope of the lines varies widely among the patients.

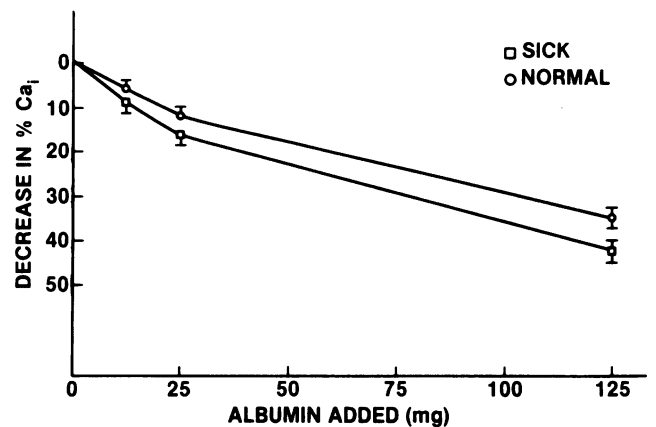


FIG. 6. Decrease in the per cent ionized calcium in serum of six critically ill (SICK) and six well (NORMAL) patients, following addition of calcium-free albumin. The curves are significantly ($p < 0.01$) different from each other at the three points plotted.

however, when elevations in these parameters were present, all the patients in our study had hypercalcemia.

The measured ionized Ca concentration is affected by the arterial pH,^{8,15,16} which alters Ca binding to protein carboxyl groups. Acute acidosis decreases protein binding (increases ionized Ca), while acute alkalosis increases protein binding (decreases ionized Ca).¹⁷ With few exceptions, patients in this study had normal pH values (Table 1), and, thus, arterial pH is unlikely to have played an important role in the insensitivity and lack of specificity between total and calculated ionized Ca and directly measured ionized Ca concentrations.

Changes in serum albumin and protein concentrations occur with alterations in posture (orthostasis) and venous stasis and are associated with changes in the total serum Ca concentrations.^{8,15} The timing and technique of venipuncture are important in the interpretation of a total serum Ca level. Depending on the nature of a meal, postprandial increases or decreases in serum Ca may occur. Prolonged use of a tourniquet during blood drawing can cause venostasis, hemoconcentration, and elevation of the total serum Ca level.¹ Heparin may reduce the serum ionized Ca concentration.^{15,18} To avoid these problems, we measured serum Ca when patients were supine and fasted and blood was drawn from in-dwelling arterial or venous catheters (no tourniquets were used) following adequate flushing with blood; we removed 5 ml of blood, then sampled the next 10 ml.

Changes in concentration of various anions can affect the serum ionized Ca level¹; however, we found no evidence of such an effect from elevated serum levels of inorganic phosphate or bicarbonate in this study. Chelation with citrate anion may cause hypocalcemia.¹⁹⁻²³ Citrate-induced decreases in serum ionized Ca correlate with circulating citrate levels and the amount of blood transfused.²¹⁻²³ Normally, citrate-induced hypocalcemia is

transient, returning to normal within 10 minutes of transfusion termination.¹⁹⁻²¹ In situations where citrate clearance is decreased (e.g., in renal or hepatic disease, hypothermia) or citrated blood infusion is rapid (>1.5 ml/kg/min), prolonged hypocalcemia may occur.²³ With one exception (see results), we found no significant serum Ca differences between patients receiving, and those not receiving, blood transfusions.

Since serum albumin binds 90% of the protein-bound Ca, one normally corrects the total serum Ca level for the serum albumin concentration. However, increased affinity of binding proteins for Ca during illness may cause the corrected total serum Ca to be underestimated. Increased affinity is suggested by the increased Ca binding to albumin (Fig. 6) and the higher K_{Ca} in the critically ill patients compared with normal controls. The sera of the critically ill patients appear to contain a factor that increases Ca binding to albumin. Factors that alter thyroid hormone binding to proteins are known to occur in non-thyroidal illness.²⁴ A decrease in K_{Ca} was found by Pedersen⁶ in patients with benign hypergammaglobulinemia and paraproteinemia. An analysis of the increase in total serum Ca for a given increase in serum albumin concentration, in 13 critically ill patients, demonstrated a large variation, suggesting different protein affinities for Ca in these patients. Since Ca and Mg bind to the same site on the albumin molecule,²⁵ we compared the serum Mg and ionized Ca concentrations and found no relationship between the two variables. Thus, variability in the affinity of Ca for binding proteins during critical illness appears to explain the poor correlation between the serum total and ionized Ca measurements.

Sepsis, malignancy, and hepatic encephalopathy were more frequently associated with hypocalcemia than eucalcemia in our ICU population. The hypocalcemia of sepsis is thought to result from parathyroid gland suppression,²⁶ while hypocalcemia in hepatic encephalopathy most likely results from failure to hydroxylate vitamin D in the liver.¹ We cannot explain why hypercalcemia was seen in our patients with hepatic encephalopathy (Table 4).

Hypomagnesemia may cause hypocalcemia by suppressing secretion of, and/or impairing the end organ response to, PTH.²⁷⁻²⁹ Excess Mg may also suppress parathyroid gland secretion.¹ In this study, abnormal Mg levels were significantly ($p < 0.05$) more common in hypocalcemic patients, with 53% having an abnormal value. Aminoglycosides may produce hypocalcemia as a result of renal losses of Mg.^{30,31} In a prospective analysis³⁰ of 55 patients receiving aminoglycoside antibiotics, we found that 38% developed hypomagnesemia and 24% became hypocalcemic (a condition responsive to Mg therapy). Cimetidine may lower serum PTH levels.³² Aminoglycosides and cimetidine were used more frequently in our hypocalcemic patients.

Renal failure was more common in the hypocalcemic than eucalcemic and hypercalcemic patients, explaining the higher serum urea nitrogen, creatinine, and phosphorus levels in the hypocalcemic patients. The primary factors responsible for hypocalcemia in renal failure are phosphorus retention and impaired 1,25-dihydroxy-vitamin D synthesis.

Intravenous $CaCl_2$, terbutaline, and narcotics were used more frequently in the hypercalcemic group. $CaCl_2$ was used in these patients as an inotropic agent. Beta-adrenergic receptor stimulation increases PTH release³³ and may partially explain the association of hypercalcemia with terbutaline in these patients. The role that opiates play in PTH or vitamin D metabolism is unclear.

Ca is required for the generation of the cardiac action potential and for excitation-contraction coupling in muscle. Low ionized Ca levels impair cardiovascular function. McLean and Hastings²⁴ noted that an isolated heart preparation stopped beating when the ionized Ca concentration of the bathing medium decreased below 2 mg/dl. Bunker et al.³⁵ reported the occurrence of hypotension, tachycardia, and depressed cardiac output in transfused patients when calculated serum ionized Ca values were 2 mg/dl or less. Das and coworkers³⁶ noted hypotension and cardiac arrhythmias in four infants when ionized Ca concentrations were <2 mg/dl (0.92–1.84 mg/dl). Killen et al.³⁷ found that ionized Ca levels below 3.4 mg/dl predisposed to death in experimental animals. Cardiovascular manifestations of hypocalcemia include congestive heart failure, hypotension, arrhythmias, and insensitivity to digitalis.¹ Two reports have substantiated the beneficial effects of correcting low ionized Ca levels in failing hearts.^{38,39} These hearts develop beta adrenergic receptor down-regulation as a result of chronic sympathetic stimulation,^{38,39} and myocardial contraction becomes heavily dependent on the maintenance of normal serum ionized Ca levels.

Hypocalcemia, in our study, was not associated with increased mortality or an increased length of ICU stay. Further study is required to determine if mild hypocalcemia is detrimental to critically ill surgical patients and which patients, if any, may benefit from replacement therapy. Porter and coworkers⁴⁰ evaluated the hemodynamic effect of a Ca infusion (1 g $CaCl_2$ over 20 min) in 10 critically ill hypocalcemic patients and found only a transient increase, followed by a reduction, in cardiac output. However, the patients were only mildly hypocalcemic (mean ionized Ca: 1.93 ± 0.08 mEq/l or 3.9 mg/dl) and had elevated cardiac outputs (mean: 9.4 ± 3.3 L/min) and MAPs (calculated from their data as 108 mmHg before calcium therapy). Henrich et al.⁴¹ evaluated cardiac contractility by two-dimensional echocardiography in eight patients on long-term hemodialysis and found that increases in ionized Ca were associated with significant increases in contractility. Further studies are also needed

to define criteria for the use of Ca as an inotropic agent in critically ill patients.

We conclude from this investigation that hypocalcemia, as determined by the total serum Ca and calculated ionized Ca values, is common in the critically ill patient. Since many critically ill surgical patients have alterations in both serum protein and arterial pH values² and since calculated ionized Ca is a poor reflection of the true measured ionized Ca, we recommend directly measuring serum ionized Ca concentrations. Variability in the affinity of Ca for serum binding proteins in critical illness may explain the poor correlation between serum total and ionized Ca measurements.

References

- Zaloga GP, Chernow B. Calcium, magnesium and other minerals. In Chernow B, ed. *The Pharmacologic Approach to the Critically Ill Patient*. Williams and Wilkins: Baltimore, 1983; 530-561.
- Chernow B, Zaloga GP, McFadden E, et al. Hypocalcemia in critically ill patients. *Crit Care Med* 1982; 10:848-851.
- Ladenson JH, Lewis JW, Boyd JC. Failure of total calcium corrected for protein, albumin and pH to correctly assess free calcium status. *J Clin Endocrinol Metab* 1978; 46:986-993.
- Sorell M, Rosen JF. Ionized calcium: serum levels during symptomatic hypocalcemia. *J Pediatr* 1957; 87:67-70.
- McLean FC, Hastings AB. The state of calcium in fluids of the body. *J Biol Chem* 1935; 108:285-322.
- Pedersen KO. Protein-bound calcium in human serum: quantitative examination of binding and its variables by a molecular binding model and clinical chemical implications for measurement of ionized calcium. *Scand J Clin Lab Invest* 1972; 30:321-329.
- Griner PF, Mayewski RJ, Mushlin AI, Greenland P. Selection and interpretation of diagnostic tests and procedures. *Ann Intern Med* 1981; 94(Part 2):557-600.
- Moore EW. Ionized calcium in normal serum, ultrafiltrates and whole blood determined by ion exchange electrodes. *J Clin Invest* 1970; 49:318-334.
- Fenton JJ, Jones M, Hartford CE. Calcium fractions in serum of patients with thermal burns. *J Trauma* 1983; 23:863-866.
- Szyfebein SK, Drop LJ, Martyn JAJ. Persistent ionized hypocalcemia in patients during resuscitation and recovery phases of body burns. *Crit Care Med* 1981; 9:454-458.
- Sorell M, Rosen JF. Ionized calcium: serum levels during symptomatic hypocalcemia. *J Pediatr* 1975; 87:67-70.
- Pittinger C, Chang PM, Faulkner W. Serum ionized calcium: some factors influencing its level. *South Med J* 1971; 64:1211-1215.
- Ladenson JH, Bowers GN. Free calcium in serum: II. Rigor of homeostatic control, correlations with total serum calcium, and review of data on patients with disturbed calcium metabolism. *Clin Chem* 1973; 19:575-582.
- Ladenson JH, Lewis JW, Boyd JC. Failure of total calcium corrected for protein, albumin, and pH to correctly assess free calcium status. *J Clin Endocrinol Metab* 1978; 46:986-993.
- Robertson WG. Measurement of ionized calcium in body fluids: a review. *Ann Clin Biochem* 1976; 13:540-548.
- Seamonds B, Towfighi J, Arvan DA. Determination of ionized calcium in serum by use of an ion-selective electrode. *Clin Chem* 1972; 18:155-160.
- Chernow B. Hormonal and metabolic considerations in critical care medicine. In Shoemaker WC, Thompson WL, eds. *Critical Care—State of the Art*, Vol 3, Fullerton: The Society of Critical Care Medicine, 1982; J1-J52.
- Ladenson JH, Bowers GN. Free calcium in serum: I. Determination with the ion-specific electrode, and factors affecting the results. *Clin Chem* 1973; 19:565-574.
- Howland WS, Schweizer O, Jascott D, et al. Factors influencing the ionization of calcium during major surgical procedures. *Surg Gynecol Obstet* 1976; 143:895-900.
- Hinkle JE, Cooperman LH. Serum ionized calcium changes following blood transfusion in anesthetized man. *Br J Anaesth* 1971; 43:1108-1112.
- Denlinger JK, Hahrwold ML, Gibbs PS, et al. Hypocalcemia during rapid blood transfusion in anesthetized man. *Br J Anaesth* 1976; 48:995-1000.
- Killen DA, Grogan EL, Gower RE, et al. Effect of ACD blood prime on plasma calcium and magnesium. *Ann Thorac Surg* 1972; 13:371-380.
- Stultz PM, Scheidegger D, Drop LJ, et al. Ventricular pump performance during hypocalcemia, clinical and experimental studies. *J Thorac Cardiovasc Surg* 1979; 78:185-194.
- Chopra IJ, Solomon DH, Chua-Teco GN, et al. An inhibitor of the binding of thyroid hormones to serum proteins is present in extrathyroidal tissues. *Science* 1982; 215:407-409.
- Pedersen KO. Binding of calcium to serum albumin: III. Influence of ionic strength and ionic medium. *Scand J Clin Lab Invest* 1972; 29:427-432.
- Taylor B, Sibbald WJ, Edmonds MW, et al. Ionized hypocalcemia in critically ill patients with sepsis. *Can J Surg* 1978; 21:429-433.
- Rude RK, Oldham SB, Sharp CF, et al. Parathyroid hormone secretion in magnesium deficiency. *J Clin Endocrinol Metab* 1978; 47:800-806.
- Rude RK, Oldham SB, Singer FR. Functional hypoparathyroidism and parathyroid hormone end-organ resistance in human magnesium deficiency. *Clin Endocrinol* 1976; 5:209-224.
- Chernow B, Smith J, Rainey TG, et al. Hypomagnesemia: implications for the critical care specialist. *Crit Care Med* 1982; 10:193-196.
- Zaloga GP, Chernow B, Pock A, et al. Hypomagnesemia is a common complication of aminoglycoside therapy. *Surg Gynecol Obstet* 1984; 158:561-564.
- Finton CK, Bjorkland S, Zaloga GP, et al. Gentamicin induced hypomagnesemia. *Am Surgeon* 1983; 49:576-578.
- Sherwood JK, Ackroyd FW, Garcia M. Effect of cimetidine on circulating parathyroid hormone in primary hyperparathyroidism. *Lancet* 1980; 1:616-620.
- Kukreja SC, Hargis GK, Bowser EN, et al. Role of adrenergic stimuli in parathyroid hormone secretion in man. *J Clin Endocrinol Metab* 1975; 40:478-481.
- McLean FC, Hastings AB. A biological method for the estimation of calcium ion concentration. *J Biol Chem* 1934; 107:337-350.
- Bunker JP, Bendixen HH, Murphy AJ. Hemodynamic effects of intravenously administered sodium citrate. *N Engl J Med* 1962; 266:372-377.
- Das JB, Eraklis AJ, Filler RM, Adams JG. Serum ionic calcium: changes with large volume blood transfusions in the infant. *J Pediatr Surg* 1971; 6:333-338.
- Killen DA, Grogan EL, Gower RE, et al. Response of canine plasma-ionized calcium and magnesium to the rapid infusion of acid-citrate-dextrose (ACD) solution. *Surgery* 1971; 70:736-743.
- Ginsburg R, Esserman LJ, Bristow MR. Myocardial performance and extracellular ionized calcium in a severely failing heart. *Ann Intern Med* 1983; 98:603-606.
- Bristow MR, Ginsburg R, Minobe W, et al. Decreased catecholamine sensitivity and β -adrenergic-receptor density in failing human hearts. *N Engl J Med* 1982; 307:205-211.
- Porter DL, Ledgerwood AM, Lucan CE, et al. Effect of calcium infusion on heart function. *Am Surgeon* 1983; 49:369-372.
- Henrich WL, Hunt JM, Nixon JV. Increased ionized calcium and left ventricular contractility during hemodialysis. *N Engl J Med* 1984; 310:19-23.