Secondary Hyperparathyroidism and Hypovitaminosis D in African-Americans with Decompensated Heart Failure

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ABSTRACT: Objective: We previously noted secondary hyperparathyroidism (SHPT) in African-American patients hospitalized during February, 2005 with either untreated or treated congestive heart failure (CHF) due to ischemic or idiopathic cardiomyopathy. Herein, we hypothesized that housebound African-American patients hospitalized during the period of June 1 through August 31, 2005, with CHF would have SHPT and hypovitaminosis D. *Methods:* Twenty-five African-American patients with an ejection fraction (EF) less than 35% due to ischemic or dilated (idiopathic) cardiomyopathy were monitored: 20 were hospitalized with CHF, stratified on historical grounds as of 4 weeks' or longer duration or of 1 to 2 weeks' duration in 11 and 9 patients, respectively, despite medical care that included furosemide; serum parathyroid hormone (PTH) and 25(OH)D at the time of admission in these patients were compared to five asymptomatic outpatients seen during the summer with stable, compensated failure. *Results:* Serum PTH was elevated (127 ± 13; 82–243 pg/mL) in all patients with CHF of 4 weeks' or longer duration (normal, 12–65 pg/mL) and was elevated in three of nine patients (59 ± 8; 18–99 pg/mL) with CHF of 1 to 2 weeks' duration. Ionized hypocalcemia (1.09 ± 0.03 and 1.08 ± 0.02 mmol/L; normal, 1.12–1.30) and hypomagnesemia (0.47 ± 0.02 and 0.46 ± 0.03 mmol/L; normal, 0.53–0.67) were respectively found in long- or short-duration CHF. No compensated patient had elevated PTH (42 ± 5; 17–53). Hypovitaminosis D (≤30 ng/mL) was universally present in patients with CHF of 4 weeks' or longer duration (15.1 ± 1.4; 7.0–23.8 ng/mL) and was also prevalent in the other groups (20.3 ± 5.1, 7.0–54.1 ng/mL in CHF of 1 to 2 weeks' duration and 23.1 ± 4.9; 17.2–42.7 ng/mL in compensated failure). *Conclusions:* In African-American patients with CHF, hypovitaminosis D, aldosteronism, and loop diuretic treatment each exaggerate Ca^{2+} and Mg^{2+} losses to stress a fragile Ca^{2+} balance leading to ionized hypocalcemia and hypomagnesemia with SHPT. **KEY INDEXING TERMS:** Parathyroid hormone; Vitamin D; Ionized hypocalcemia; Ionized hypomagnesemia; African-Americans; Congestive heart failure. **[Am J Med Sci 2006; 332(3):112–118.]**

Congestive heart failure (CHF), a salt-avid clinical syndrome, is accompanied by an activation of the circulating renin-angiotensin-aldosterone system,[1–6] the presence of oxidative stress in such diverse tissues as skin, skeletal muscle, heart, and peripheral blood mononuclear cells (PBMC),[7–11] an immunostimulatory state with activated PBMC and such proinflammatory cytokines as interleukin-6 and tumor necrosis factor (TNF)-α,[12–18] and a wasting of soft tissue and bone.[19–23] Pathophysiologic responses involved in the appearance of this systemic illness are under investigation. Our working hypothesis has originated from a rat model of aldosteronism, in which plasma aldosterone (ALDO) levels are inappropriately (relative to dietary Na^+) raised to those seen in human CHF. Secondary hyperparathyroidism (SHPT) is invoked in these rats with parathyroid hormone (PTH)–mediated intracellular Ca^{2+} overloading of multiple cell types, not unlike responses that accompany SHPT in cases of chronic renal failure.[24,25] Oxidative stress is induced in Ca^{2+}-loaded lymphocytes and monocytes, leading to their autoactivation and a proinflammatory phenotype, which can be prevented by parathyroidectomy, a Ca^{2+} channel blocker, or an antioxidant.[24–28] The presence

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Submitted March 29, 2006; accepted in revised form May 26, 2006.

Presented at the 2006 Southern Regional Meeting for the Society for Clinical Investigation.

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of SHPT with elevated plasma PTH level in these rats is further confirmed by bone resorption and is preventable by parathyroidectomy.[24,26,29] The appearance of SHPT in aldosteronism occurs in response to sustained increments in urinary and fecal excretion of Ca^{2+} and Mg^{2+} and a consequent reduction in their extracellular concentrations, the enhanced excretion of which at both sites can be prevented by spironolactone, an ALDO receptor antagonist.[24,26,30–34] Hyperparathyroidism, which is associated with elevated circulating levels of interleukin-6 and TNF-α,[35,36] has been reported in patients with primary aldosteronism, in whom associated abnormalities in circulating Ca^{2+} and PTH can be corrected by spironolactone or adrenal surgery.[37–40]

The suspicion of SHPT in human cases of CHF has been based on 18% to 40% of predominantly white patients with advanced symptomatic failure awaiting cardiac transplantation having elevated serum PTH levels,[21,22,41–45] and where secondary aldosteronism is a well-known component of salt and water retention.[1–6] We recently reported elevated serum PTH levels in African-American patients consecutively hospitalized during the winter (February, 2005) with chronic untreated and treated decompensated heart failure (NYHA Class III–IV).[46] The contribution of hypercalciuria and hypermagnesuria promoted by long-term treatment with furosemide, a potent loop diuretic, may also be participatory to the appearance of SHPT.[47] A role for hypovitaminosis D due to reduced sunlight exposure in housebound, symptomatic patients with CHF must also be taken into account. Reduced circulating levels of 25(OH)D, a marker of compromised vitamin D stores, have been reported in some patients of a predominantly white population awaiting cardiac transplantation in Zurich and New York City and among some patients who were studied during the winter in North Rhine-Westfalia.[22,42,44] In African-Americans, melanin is a natural sunscreen that raises the time requirement for sunlight exposure;[48] therefore, one might postulate that hypovitaminosis D might also be particularly contributory in African-American patients with CHF.

Herein we hypothesized the presence of SHPT with hypovitaminosis D in symptomatic African-American patients having systolic dysfunction and who, despite medical management that included furosemide, were hospitalized during the period of June 1 through August 31, 2005, because of clinical symptoms and signs of decompensated heart failure and in whom elevations in plasma renin activity and ALDO are known to be present.[1–6] Given the importance of sustained elevations in serum ALDO in promoting urinary and fecal losses of Ca^{2+} and Mg^{2+}, these patients were further stratified as to their CHF being of long (≥4 weeks) or short (1–2 weeks) duration. Serum PTH and 25(OH)D levels in these two groups were compared to asymptomatic or minimally symptomatic African-American outpatients with compensated heart failure (NYHA Class I and II), who were seen during this time frame and in whom serum ALDO is known to be normal.[2]

Methods

Patient Population

Our study population consisted of 25 patients, all of whom were African-American. Twenty of these patients were admitted to the Cardiology Service at the Regional Medical Center (or MED) in Memphis (latitude 35°N to 36°41′N) from June 1 to August 31, 2005 because of their CHF due to either an ischemic or dilated (idiopathic) cardiomyopathy. Five outpatients followed in the MED Cardiology Clinic with stable, compensated heart failure were also included. All 25 patients had echocardiographic evidence of systolic dysfunction as reflected by an ejection fraction of less than 35% (9–30%). Based on historical information provided by the patients regarding their symptomatic status (e.g., duration and progressive nature of lower extremity edema, orthopnea, paroxysmal nocturnal dyspnea), 11 of these patients were considered to have protracted (≥4 weeks) CHF (NYHA Class III and IV). In nine patients, the duration of the CHF was of shorter duration (1–2 weeks). The reported duration of symptomatic failure was used to infer the chronicity to the elevation in their serum ALDO.

Among the 11 patients with decompensated CHF for 4 weeks or longer, there were 5 men and 6 women ranging in age from 38 to 79 years (mean ± SEM: 54.2 ± 3.7 yrs) with systolic dysfunction due to ischemic cardiomyopathy in two, while nine had a dilated (idiopathic) cardiomyopathy. In the nine patients with decompensated CHF of 1 to 2 weeks' duration, there were 7 men and 2 women (46.0 ± 3.4; 31–59 yrs), with 8 having a dilated (idiopathic) cardiomyopathy. Because of their symptomatic status, all patients with CHF noted reduced outdoor activities.

The 11 patients with decompensated CHF for 4 weeks or longer were receiving either an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), together with daily furosemide (82 ± 10 mg), for months prior to and at the time of admission. Five of them had also been receiving a small (25 mg) dose of spironolactone. Of the nine patients with short-term decompensated CHF, all were receiving an ACE inhibitor or ARB prior to admission, whereas four had been receiving daily furosemide (58 ± 10 mg) for several weeks.

The third group consisted of five outpatients seen during the summer of 2005 who had comparable systolic dysfunction due to either ischemic (one) or idiopathic (four) cardiomyopathy without physical findings of intra- or extravascular volume expansion and who were asymptomatic except in situations of moderate to heavy workloads and therefore were considered to have compensated heart failure (NYHA Class II and I, respectively). This group consisted of four men and one woman (51.2 ± 5.1; 43–70 yrs). Four of these people were receiving an ACE inhibitor and small-dose spironolactone and three were also receiving daily furosemide (93 ± 13 mg). The study was approved by this institution's review board, with the vitamin D assay considered a standard of care in housebound patients.

Serum Parathyroid Hormone and 25(OH)D

Blood for determination of PTH and 25(OH)D was obtained in the morning during the first 48 hours of admission, whereas in outpatients it was obtained during the afternoon of the patient's clinic visit.

Calculated creatinine clearance was based on the Cockroft-Gault formula[49] using serum creatinine obtained at the time of hospital discharge or on an outpatient basis.

Serum-Ionized $[Ca^{2+}]_o$ and $[Mg^{2+}]_o$

Concentrations of serum-ionized $[Ca^{2+}]_o$ and $[Mg^{2+}]_o$ were determined in patients with protracted or shorter duration CHF by the direct ion-selective electrode technique with a Nova 8 Analyzer (Nova Biomedical, Waltham, MA) and expressed in millimoles per liter, as previously reported.[24,26]