Macro- and micronutrients in patients with congestive heart failure, particularly African-Americans

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Abstract: Not all patients with heart failure, defined as a reduced ejection fraction, will have an activation of the RAAS, salt and water retention, or the congestive heart failure (CHF) syndrome. Beyond this cardiorenal perspective, CHF is accompanied by a systemic illness that includes oxidative stress, a proinflammatory phenotype, and a wasting of soft tissues and bone. A dyshomeostasis of calcium, magnesium, zinc, selenium, and vitamin D contribute to the appearance of oxidative stress and to compromised endogenous defenses that combat it. A propensity for hypovitaminosis D, given that melanin is a natural sunscreen, and for secondary hyperparathyroidism in African-Americans make them more susceptible to these systemic manifestations of CHF—a situation which is further threatened by the calcium and magnesium wasting that accompanies the secondary aldosteronism of CHF and the use of loop diuretics.
Keywords: African-Americans, heart failure, calcium, magnesium, zinc, selenium

Introduction

Approximately 4.8 million Americans suffer from congestive heart failure (CHF) with an estimated 400,000 new cases diagnosed each year. Congestive heart failure is a clinical syndrome based on left ventricular dysfunction which results in salt and water retention and effort incapacity mediated by hormonal factors, most notably the renin-angiotensin-aldosterone and the sympathetic nervous systems (Anand et al 1989; Francis et al 1990; Swedberg et al 1990; Villarreal et al 1993; Weber 2001; Jessup and Brozena 2003). While pharmacologic blockade of these systems improves survival and quality of life (The SOLVD Investigators 1991; Pitt et al 1999), less well recognized are the roles played by micronutrients such as vitamins, zinc and selenium, and macronutrients, especially calcium and magnesium.

Oxidative stress

An important component of the CHF syndrome is the generation of cytotoxic reactive oxygen and nitrogen species, together with a reduction in antioxidant defenses (Molavi and Mehta 2004; Wykretowicz et al 2004; Ungvari et al 2005). Two such defenses are Cu/Zn-superoxide dismutase (SOD) and Se-glutathione peroxidase (GSH-Px), which serve as O_2^- and H_2O_2 scavengers (Itoh et al 2004) and are dependent upon zinc and selenium bioavailability (Xia et al 1989; Thakur et al 2004). Secondary hyperparathyroidism, a covariant of chronic renal failure due to hypovitaminosis D and the resultant inability to absorb calcium from the intestine, is also common in patients with heart failure (Lee et al 1994; Shane et al 1997; Arroyo et al 2006; Khouzam et al 2006; LaGuardia et al 2006). The secondary hyperparathyroidism due to reduced plasma-ionized Ca^{2+} and Mg^{2+} secondary to increased urinary and fecal calcium excretion is noted in rats administered aldosterone in quantities one would expect to find in

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CHF (Chhokar et al 2004; Chhokar et al 2005). Secondary hyperparathyroidism not only increases bone resorption to free up calcium and magnesium but paradoxically drives calcium intracellularly, a potent stimulus for oxidative and nitrosative stress.

Macronutrient deficiency in congestive heart failure

Shane et al (1997) evaluated 101 predominantly Caucasian patients with severe (NYHA class III or IV) CHF referred for cardiac transplantation. Serum 25 hydroxyvitamin D (25(OH)D), 1,25-dihydroxyvitamin D ($1,25(OH)_2D_3$), and intact parathyroid hormone (PTH) were monitored. 25(OH)D and $1,25(OH)_2D_3$ levels were reduced in 17% and 26% of these patients, respectively, while PTH levels were elevated in 30%. Likewise, Stefenelli et al (1992) also found elevated PTH levels in 5 of 27 Caucasian patients (18.5%) with advanced CHF. As noted above, experimental studies of aldosteronism in rats have demonstrated urinary and fecal losses of calcium together with excessive intracellular calcium accumulation and increased H_2O_2 production. Calcium, as well as magnesium, sodium, and potassium are examples of macronutrients, and as such are crucial for homeostasis. In the study by Shane et al there is, not surprisingly in light of the lower 25(OH)D and $1,25(OH)_2D_3$ levels and calcium loss, clear evidence of increased bone turnover.

Loop diuretics such as furosemide have been shown to adversely affect calcium and bone homeostasis. Stein et al (1996) assessed serum 25(OH)D, PTH, creatinine, and a variety of medications, including loop diuretics, in 251 nursing home residents. Fifty-two percent had 25(OH)D reduced below the normal level, and PTH above the upper limit of the reference value. Daily furosemide dosing was an important predictor of elevated PTH levels. In summary, both animal and clinical data support the contention that CHF is associated with secondary hyperparathyroidism, most likely accentuated by the use of loop diuretics.

African-Americans and hypovitaminosis D

Because of the higher melanin content in the skin of African-Americans, which serves as a sunscreen, one would expect a relatively suboptimal production of vitamin D. Perry et al (1993) measured 25(OH)D, PTH, osteocalcin, and calcitonin levels in 32 African-Americans aged 68–93, and in 43 white Americans aged 70–89, none of whom were receiving thiazide diuretics. Thirty-eight percent of the African-American men and 38% of the African-American women had 25(OH)D levels <8 ng/mL, compared to 22% of the Caucasian men and 40% of Caucasian women. PTH was above the normal range in 25% of the African-American men and 33% of the African-American women compared to 14% and 30%, respectively, for the Caucasian men and women. Bikle et al (1999) assessed 25(OH)D levels, during the summer and winter months, in 109 black men, 114 white men, 95 black women, and 84 white women. Not only were 25(OH)D levels lower among the black subjects, but the values of this essential vitamin were 19%–29% lower in the winter than in the summer irrespective of race and gender. Fuleihan et al (1994) studied the response of PTH to hypo- and hypercalcemia in six healthy white and six healthy black volunteers, with results showing incremental values of 9.2 and 0.7 pmol/L among the African-Americans, and 6.9 and 0.3 pmol/L among the Caucasian subjects. These authors concluded that African-Americans demonstrate a greater propensity to express mild hyperparathyroidism under a provocative hypocalcemic challenge.

African-Americans with congestive heart failure; incidence of secondary hyperparathyroidism

Khouzam et al (2006) monitored serum PTH and calcium levels in 9 patients, hospitalized with CHF and left ventricular systolic dysfunction (ejection fraction <35%), 8 of whom were African-Americans. In all patients, serum PTH levels were consistently elevated above the reference value (65 pg/mL) despite normal calcium levels. In 5 patients with previously untreated CHF, plasma PTH ranged from 86 to 393 pg/mL, whereas PTH in the 4 patients with previously treated CHF ranged from 105–164 pg/mL. Arroyo et al. (2006), from the same group, studied 40 African-American patients with CHF divided into protracted (≥4 weeks, 15 inpatients), shorter duration (1–2 weeks, 15 inpatients), and compensated (10 outpatients). The serum PTH was elevated in all of the patients with protracted failure, in 60% of the patients with shorter duration failure, and in none of the compensated group. Likewise, serum-ionized calcium and magnesium concentrations were reduced in the "decompensated" groups. Hypovitaminosis D, with serum 25(OH)D levels <30 ng/mL, was found in all protracted heart failure patients and in 80% of the group with symptoms for 1–2 weeks. Eighty percent of the compensated patients were found to have subnormal 25(OH)D levels, whereas 9 African-American volunteers without evidence of cardiovascular

disease serving as controls tested euparathyroid with normal 25(OH)D values. Thus, CHF in African-Americans is associated with secondary hyperparathyroidism, with inadequate exposure to sunlight appearing to be an attractive but unproven etiology for this condition. Other etiologic factors are aldosteronism with elevated urinary and fecal losses of calcium, and the calciuric effect of loop diuretics.

Micronutrient deficiencies in aldosteronism and congestive heart failure

Micronutrients exist only in minute amounts and function in their primary role as coenzymes in antioxidant reactions. Zinc, copper, and selenium are all examples of micronutrients, the primary source of which is dietary. Zinc deficiency has been well described in conditions of stress, such as sepsis, trauma, and malnutrition; these conditions are associated with a decline in Cu/Zn-SOD activity, an important antioxidant defense (Thakur et al 2004). When rats are administered aldosterone to raise serum levels to those one would expect in CHF, they exhibit significant zincuria together with depressed activity of Cu/Zn-SOD (Thomas et al 2007). Ripa et al (1998) investigated the relationship between CHF and zinc and copper levels in blood, urine, and red blood cells in normal volunteers, in 15 patients with dilated cardiomyopathy, and in 11 patients with hypertrophic cardiomyopathy. Zincuria with low plasma and erythrocyte zinc levels was found in patients with dilated cardiomyopathy, whereas plasma and erythrocyte levels were depressed in those with hypertrophic cardiomyopathy without zincuria. The authors speculate a causative role for an atrial natriuretic peptide in promoting zincuria. CHF may be associated with a deficiency of plasma zinc; medications, particularly angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, result in an increased urinary excretion of zinc (Cohanim and Yendt 1975; Wester 1980; Zumkley et al 1985; Abu-Hamdan et al 1988; Koren-Michowitz et al 2005). The role of nutrient supplementation in CHF, particularly that of zinc and selenium, is not well appreciated at this time, but warrants investigation.

Selenium is an important cofactor in antioxidant enzymatic reactions which aid cellular and humoral immunity (Kidd 2003). Selenium deficiency is associated with cardiomyopathy in a certain area of China, the Keshan province, where selenium is depleted in the soil, and in patients receiving parenteral nutrition without selenium supplementation (Quercia et al 1984; Xia et al 1989; Oster 1993; Levy et al 1994; Huttunen 1997; Vijaya et al 2000). A cardiomyopathy linked to selenium deficiency is so endemic to Keshan province of China that the disease now bears the name of this area. Xia et al (1989) sampled blood from healthy young men from Dechang County, China, for selenium levels and glutathione peroxidase activity, and compared these values to those from subjects from Mianning County, where sodium selenite is added to salt and Keshan disease is rare. Plasma selenium concentrations from the Dechang group were 33 and 38% (boys and men) those of the Mianning group. Likewise, the glutathione peroxidase activity from Dechang (boys and men) was 33% and 43% that of the Mianning group. Daily selenium supplementation (100 mcg for boys and 200 mcg for men) improved these values, implying that Keshan disease may be prevented or ameliorated. However, the role of selenium deficiency in atherosclerotic coronary disease remains controversial (Huttunen 1997).

Levy et al (1994) reported a case of reversible cardiomyopathy in a patient receiving selenium-deficient parenteral nutrition. Quercia et al (1984) measured selenium concentrations in plasma, heart, kidney, and liver from a patient who died of a cardiomyopathy while receiving long-term intravenous nutrition. Such values were 5%–12% of normal values. The role of selenium deficiency in more usual forms of dilated cardiomyopathy not associated with parenteral nutrition has been less well investigated. Vijaya et al (2000) measured serum selenium values in 37 patients with dilated cardiomyopathy, and found that these values were 27% those of the normal controls. This study did not address other risk factors, but there was a high incidence of alcohol intake among their patients.

Congestive heart failure is associated with deficiencies of plasma zinc and selenium. The etiology of such deficiencies is multifactorial, including medications and malnutrition; the role of micronutrient supplementation as a therapy for this syndrome has not been investigated.

Micronutrient deficiencies in African-Americans with congestive heart failure

Arroyo et al (2006) in the aforementioned study of 40 African-American patients with protracted, short-lived, and compensated CHF, examined serum zinc and selenium values. In the protracted group, 70% were hypozincemic and 100% exhibited selenium values below normal. Such values among the short-lived group were 50% and 60% respectively, compared to 50% and 100% in the compensated

outpatient group. Thus, micronutrient values not only reflect the condition of CHF, but may indicate its severity.

Summary and conclusion

Congestive heart failure is a state of aldosteronism characterized by salt and water retention; catecholamine excess is another key component of this syndrome. Less well recognized is the presence of altered calcium levels, parathyroid homeostasis with hypovitaminosis D and secondary hyperparathyroidism, particularly in African-Americans. The mechanisms of secondary hyperparathyroidism and hypovitaminosis D are multiple. For example, aldosterone excess leads to increased urinary and fecal calcium losses with a resultant fall in serum-ionized Ca^{2+} and Mg^{2+}, thereby stimulating parathyroid secretion. Furthermore, loop diuretics cause calciuria and magnesuria. Sunlight is critical to vitamin D synthesis and lack of its exposure to bare skin becomes a crucial issue in patients with symptomatic CHF who are likely to be home- or hospital-bound. The increased melanin content of the skin of African-Americans causes a relative resistance to sunlight making them more at risk of hypovitaminosis D. The role of sunlight or ultraviolet B light exposure in the treatment of this syndrome remains to be investigated.

Hypozincemia and hyposelenemia are commonly observed in CHF patients, particularly African-Americans, and a deficiency of these antioxidant cofactors can lead to oxidative stress. Malnutrition is the most likely etiology for micronutrient deficiencies, although angiotensin-converting enzyme inhibitors and angiotensin receptor blocking agents cause hyperzincuria. Based upon the experience with zinc supplementation in patients receiving parenteral nutrition, one would expect a direct benefit from dietary supplementation.

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