

CONGESTIVE HEART FAILURE AND VITAMIN D DEFICIENCY

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Introduction

Congestive heart failure (CHF) is a chronic medical condition whose incidence is rising. The prevalence of CHF is approximately 1% to 3% in Western countries.¹ Despite innovations in medical therapy, CHF is associated with high morbidity and mortality rates.²

CHF patients commonly experience muscle weakness and fatigue as two major symptoms. An altered intracellular handling of ionized calcium has been suggested to play a vital role in impaired myocardial contraction.³ In isolated myocytes from patients with end stage heart failure, systolic ionized calcium levels were markedly decreased, while diastolic levels were elevated as compared to healthy controls.⁴ In addition, digitalis and beta-blocker medical therapy is frequently used in CHF patients and is known to increase myocardial ionized calcium levels.⁵

Vitamin D Sources and Action

Solar ultraviolet B radiation penetrates the skin and converts 7-dehydrocholesterol to previtamin D₃ which is then converted to vitamin D₃. Vitamin D₃ is then metabolized in the liver to 25-OH vitamin D. This is often used to determine a patient's vitamin D status. 25-OH vitamin D is converted in the kidneys to its active form 1,25-OH vitamin D, and this conversion is regulated by parathyroid hormone levels, serum calcium and phosphorus levels.⁶

People get vitamin D from sunlight exposure, diet, and dietary supplementation. Only a few foods such as eel, herring, and salmon are good sources of vitamin D. Fortunately, ultraviolet B-induced synthesis of vitamin D is extremely effective.

More than 200 genes, which regulate cellular proliferation, differentiation, apoptosis, and angiogenesis, are either directly or indirectly controlled by 1,25-OH vitamin D.⁷ It is also associated with increased insulin production,⁸ decreased renin synthesis and increased myocardial contraction.

Receptors for the vitamin D hormone (VDR) exist in a variety of cell types including osteoblasts, myocytes, cardiomyocytes, pancreatic cells, endothelial cells, neurons, and immune cells. *In vitro* studies demonstrate that vitamin D suppresses pro-inflammatory cytokines (e.g., IL-6, IL-2, interferon-gamma, TNF-alpha) and upregulates levels of the anti-inflammatory cytokine (e.g., IL-10).⁹

Epidemiology of Vitamin D Deficiency

The different stages of vitamin D status can be classified as deficiency, insufficiency, hypovitaminosis, adequacy and toxicity. Vitamin D deficiency is associated with severe clinical symptoms such as rickets, osteomalacia, myopathy, and calcium malabsorption. In vitamin D insufficiency biochemical alterations such as mild hyperparathyroidism and low intestinal calcium absorption are noted without severe clinical symptoms. In addition, calcitriol levels remain normal at the expense of

elevated parathyroid hormone.¹⁰ In hypovitaminosis D, the body stores of vitamin D are already low but only minor physiological abnormalities, such as an elevated PTH level are seen.¹¹ In vitamin D adequacy there are no disturbances in dependent bodily functions. Finally, in vitamin D toxicity there is intestinal calcium hyperabsorption and increased bone resorption which leads to hypercalcemia.

In the National Health and Nutrition Examination Survey (NHANES III), low 25-OH vitamin D levels were associated with multiple medical problems including coronary vascular disease, cancer, congestive heart failure, hypertension and diabetes.¹² Although there is no consensus, many researchers believe an optimal level of 25-OH vitamin D to be 30ng/mL or more.¹³ With this number, it has been estimated that 1 billion people worldwide have vitamin D deficiency or insufficiency.¹⁴ Unfortunately, 41% of men and 53% of women in the United States (U.S.) have levels of 25-OH vitamin D below 28ng/mL.¹⁵ In the elderly population in the U.S. and Europe that are still living in the community (not in nursing homes) 40% to 100% are vitamin D deficient.¹⁶

Risk factors for developing vitamin D deficiency include sunscreen usage, dark skin, breast fed infants, aging, inflammatory bowel disease, fat malabsorption disease, obesity and a sedentary lifestyle.¹⁷ Severe deficiency often develops in completely immobile patients.¹⁸ Interestingly, one study found that 93% of people presenting to an emergency department with complaints of muscle aches and bone pain and who had a vast array of medical diagnoses were deficient in vitamin D.¹⁹ Circulating levels of 25-OH vitamin D depend largely on exposure to ultraviolet B light. Serum 25-OH vitamin D levels decrease with age because of the diminishing capability of the skin to produce previtamin D.²⁰

Vitamin D Deficiency and CHF

In many patients CHF is the end stage of hypertensive, coronary, and valvular cardiovascular disease. There is increasing evidence to support the notion that low vitamin D status may be an important factor in the development and pathogenesis of CHF. Patients with CHF have reduced circulating levels of 25-OH vitamin D and calcitriol and increased levels of serum phosphorus and PTH.²¹ In an observational study, patients with severe CHF were found to have vitamin D deficiency as well as hyperparathyroidism.²² Excess PTH levels increase blood pressure and cardiac contractility and lead to hypertrophy of cardiac myocytes and interstitial fibrosis.²³ Serum 25-OH vitamin D is a major factor in determining the plasma level of PTH in normal and CHF patients.²⁴

In addition, cardiac muscle cells have a vitamin D receptor and a calcitriol-dependent ionized calcium binding protein.²⁵ In experimental vitamin D deficiency models, calcitriol adminis-

tration can normalize impaired myocardial contractility.²⁶ Calcitriol is also known to be a negative endocrine regulator of the renin-angiotensin-aldosterone system (RAAS), which when inappropriately stimulated results in hypertension.²⁷ A case report demonstrated that intravenous calcitriol treatment decreased the plasma activity of renin and angiotensin II, lowered blood pressure and reversed myocardial hypertrophy.²⁸ In one study of hypertensive patients, who were exposed to ultraviolet B radiation three times a week for three months had a 180% increase in 1,25-OH vitamin D and both systolic and diastolic blood pressure reduced by 6mmHg.²⁹

CHF patients have been shown to have significantly lower 25-OH vitamin D levels during the winter months (November-April) than during the summer months (May-October) which are results similar to healthy controls.³⁰ However, CHF patients have low outdoor activity due to disease symptoms and thus have limited opportunity to generate adequate previtamin D from the skin. This limitation may potentiate or worsen their clinical condition during the winter months.

Interestingly, Zittermann *et al* report data in an unpublished case control study that suggests that lifestyle factors that influence vitamin D differ during childhood, adolescence and adulthood in CHF patients versus controls. This data suggests that patients have a low vitamin D status in these ages even when they are free from CHF.³¹

The Future

As the incidence of congestive heart failure increases in the U.S. population, a greater focus will be needed to better elucidate the role of Vitamin D in the pathogenesis of symptoms. Further research, in the form of randomized controlled trials is necessary to determine whether Vitamin D supplementation can reduce the progression of heart failure. In the near future it is important to determine whether Vitamin D can be used as a marker of disease progression.

References

- McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *NEJM* 1971; 285:1441-1446.
- Bleumink GS, Knetsch AM, Sturkenboom MC et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. *European Heart Journal* 2004;25:1614-1619.
- Kruger C, Erdmann E, Nabauer M et al. Intracellular calcium handling in isolated ventricular myocytes from cardiomyopathic hamsters (strain BIO 14.6) with congestive heart failure. *Cell Calcium* 1994; 16:500-508.
- Beuckelmann DJ, Nabaer M, Erdmann E. Intracellular calcium handling in isolated ventricular myocardium. *Circulation* 1992; 85:1046-1055.
- Colucci WS, Wright RF, Braunwald E. New positive inotropic agents in the treatment of congestive heart failure. Mechanisms of action and recent clinical developments. *NEJM* 1986; 314:290-299.
- Holick MF. Vitamin D deficiency. *NEJM* 2007;357(3):266-281.
- Holick MF. Resurrection of vitamin D deficiency and rickets. *Jour Clin Invest* 2006; 116:2062-2072.
- Chiu KC, Chu A, Go VLW et al. Hypovitaminosis D is associated with insulin resistance and Beta cell dysfunction. *Amer Journ Clin Nutr* 2004; 79:820-825.
- Zhu Y, Mahon BD, Froicu M, et al. Calcium and 1alpha,25-dihydroxyvitamin D3 target the TNF-alpha pathway to suppress experimental inflammatory bowel disease. *European Journal of Immunol* 2005;35:217-224.
- Lips P, Hackeng WHL, Jongen MJM et al. Seasonal variation in serum concentrations of parathyroid hormone in elderly people. *Journal of Clinical Endocrinol Metab* 1983; 57:204-206.
- Gomez-Alonso C, Naves-Diaz ML, Feernandez-Martin JL, et al. Vitamin D status and secondary hyperparathyroidism: the importance of 25-hydroxyvitamin D cut-off levels. *Kidney International* 2003; 85:Suppl:44-48.
- Melamed ML, Michos ED, Post W, et al. 25-hydroxyvitamin D levels and the risk of mortality in the general population. *Arch Internal Medicine* 2008; 168(15):1629-1637.
- Thomas MK, Lloyd-Jones Dm, Thadhani RI, et al. Hypovitaminosis D in medical inpatients. *NEJM* 1998;338(12):777-783.
- Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* 2006;81:353-373.
- Zadshir A, Tareen N, Pan D, et al. The prevalence of hypovitaminosis D among US adults: data from NHANES III. *Ethn Disease* 2005;15(4) Suppl(S5):97-101.
- Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* 2006; 81:353-373.
- Zittermann A, Sabatschus O, Jantzen S, et al. Exercise-trained young men have higher calcium absorption rates and plasma calcitriol levels in comparison to age-matched sedentary controls. *Calcif Tissue Int* 2000; 67:215-219.
- McKenna M. Differences in vitamin D status between countries in young adults and elderly. *American Journal of Medicine* 1992; 93:69-77.
- Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. *Mayo Clinic Proc* 2003; 78:1463-70.
- MacLaughlin J, Holick MF. Aging decreases the capacity of the human skin to produce vitamin D3. *Journal of Clin Invest* 1985;76:1536-1538.
- Zittermann A, Schleithoff SS, Tenderich G et al. Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure. *American College of Cardiology* 2003; 41(1):105-112.
- Shane E, Mancini D, Aaronson K, et al. Bone mass, vitamin D deficiency, and hyperparathyroidism in congestive heart failure. *American Journal of Medicine* 1997; 103:197-207.
- Rostand SG, Drucke TB. Parathyroid hormone, vitamin D, and cardiovascular disease in chronic renal failure. *Kidney Int* 1999; 56:383-392.
- Pepe J, Romagnoli E, Norfroni L, et al. Vitamin D status as the major factor determining the circulating levels of parathyroid hormone: a study in normal subjects. *Osteoporosis Int* 2004;16:805-812.
- Thomasset M, Parkes CO, Cuisinier-Gleizes P. Rat calcium-binding proteins: distribution, development, and vitamin D dependence. *American Journal of Physiology* 1982; 243:E483-488.
- Hochhauser E, Barak J, Kushnir T et al. Mechanical, biochemical, and structural effects of vitamin D deficiency on the chick heart. *Angiology* 1989;40:300-308.
- Li YC. Vitamin D regulation of the renin-angiotensin system. *Journal of Cell Biochem* 2003; 88:327-331.
- Park CW, Oh YS, Shin YS, et al. Intravenous calcitriol regresses myocardial hypertrophy in hemodialysis patients with secondary hyperparathyroidism. *American Journal of Kidney Diseases* 1999; 33:73-81.
- Krause R, Buhring M, Hopfenmuller W, et al. Ultraviolet B and blood pressure. *Lancet* 1998; 352:709-710.
- Zittermann A. Vitamin D in preventive medicine – are we ignoring the evidence? *British Journal of Nutrition* 2003; 89: 552-572.
- Zittermann A, Schleithoff SS. Vitamin D insufficiency in congestive heart failure: why and what to do about it? *Heart Failure Reviews* 2006; 11:25-33.