

Vitamin D Deficiency and Cardiovascular Risk: we're still in the Dark

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For decades, observational studies has provided evidence of the association between reduced levels of 25-hydroxy vitamin D and increased risk of cardiovascular disease. It is generally accepted that vitamin D deficiency is in some way related to adverse cardiovascular outcomes [1,2]. It has been postulated that this association may be a result of reverse causality in which unhealthy and less mobile individuals are less likely to be exposed to sunlight [3], or perhaps due to a physiological chain of events in which low vitamin D concentrations promote downstream vascular remodeling and hemodynamic instability [4,5].

And yet, after thousands of studies have been published on the topic, the global medical community remains very much in the dark regarding whether a true relationship exists between vitamin D deficiency and increased cardiovascular risk. A small number of clinical trials which have aimed to assess the possibility of a direct, causal relationship between low vitamin D concentrations and poor cardiovascular outcomes in select patient populations do exist. Unfortunately, meta-analyses of these trials demonstrate widespread inconsistency in trial duration, sample size, type of vitamin D intervention and route of administration, and primary outcomes [6-8]. As a result, the medical landscape is barren of vitamin D trials with consistent, pragmatic designs formulated a priori to assess cardiovascular outcomes and thus the depth of knowledge of vitamin D has remained stagnant [6].

One large patient population may be able to shine a much-needed spotlight on this topic. Individuals with chronic kidney disease (CKD), specifically those with end-stage kidney disease requiring dialysis, experience dramatically increased risk of cardiovascular disease compared to that of the general population [9]. In addition, the progressive loss of kidney function also results in disruption of regular vitamin D metabolism, thus the prevalence of severe vitamin D deficiency in this patient population is extremely high [10]. The concomitant nature of high cardiovascular risk and severe vitamin D deficiency persistent in CKD provides a unique opportunity to analyze this seemingly complex physiological relationship.

In general, approximately 25% of all deaths in CKD are attributed to Sudden Cardiac Arrhythmic death (SCD) [9,11], which results primarily from miscommunication between the sympathetic and parasympathetic branches of the cardiac Autonomic Nervous System (ANS) and the atrio-ventricular and sino-atrial nodes of the heart [12,13]. Changes in sinus rhythm controlled by the electrical signals passed from the ANS to the heart can be quantified by measuring Heart Rate Variability (HRV) with a typical ambulatory heart monitor [14]. Measures of HRV in CKD patients often demonstrate a dramatic shift in ANS activity, in which the heart is predominantly regulated by excitatory sympathetic signaling couple by extreme withdrawal in inhibitory, cardio-protective parasympathetic control [15,16]. This characteristic imbalance in HRV has been associated with the increased risk of SCD in this patient population [15,16]. Interestingly, observational studies have shown evidence of a link between vitamin D deficiency and abnormal HRV in humans both with and without CKD [17,18], as well as an improvement in HRV responses to a vascular stressor following 4 weeks of intensive oral vitamin D supplementation [19]. These findings suggest that vitamin D may play a role in regulating

the activity of the cardiac ANS, and therefore may directly impact cardiovascular and SCD-specific risk to some degree in humans.

Looking further into the CKD population, it becomes apparent that the concentration of serum 25-hydroxy vitamin D may not hold all of the answers. Thoughtful and concise studies by Wolf and colleagues [20,21] have demonstrated that higher levels of activated 1,25-dihydroxy vitamin D, rather than 25-hydroxy vitamin D, are very strongly associated with decreased risk of cardiovascular mortality in the CKD population. Because 1,25-dihydroxy vitamin D is produced mainly in the proximal tubules of the functional kidneys and it therefore chronically low in patients with CKD [20], this data would suggest that activated vitamin D concentrations may drive the observed relationship between vitamin D deficiency and increased cardiovascular risk via the disruption of cardiac ANS regulatory function. Lending to this thought, the aforementioned observational studies also showed that cardio-protective parasympathetic activity was dramatically restored only in subjects who achieved the highest quartile of 1,25-dihydroxy vitamin D levels after 4 weeks of oral supplementation [19].

Clinical trials to assess the plausible causal relationship between low 1,25-dihydroxy vitamin D and cardiac ANS activity as a surrogate marker of cardiovascular risk are far and few between. Results of one completed study, the VITAH Trial, have not yet been published [22]. Basic science investigations have also played a role in helping to expose the nature of the relationship between vitamin D, the cardiac ANS, and cardiovascular risk. While 25-hydroxy vitamin D is viewed as the barometer of vitamin D status, activated 1,25-dihydroxyvitamin D holds a much greater affinity for the vitamin D receptor and is therefore much more effective at eliciting its desired target responses [23]. Interestingly, activated vitamin D is capable of crossing the blood-brain barrier in order to interact with neurons and cells within the nervous system [24,25]. Vitamin D receptors have been located in high concentrations within the mid-brain and brainstem structures that house the preganglionic nerves of the ANS [24]. Neuronal cells with exposure to high concentrations of 1,25-dihydroxy vitamin D have been shown to better regulate the transcription, production, and release of neurotransmitters which act to regulate signal transduction between the ANS and the heart, among other organs [24,25]. From a biological standpoint, there is a clear indication that activated vitamin D could directly interact with the ANS to elicit changes in sympathetic and parasympathetic signaling. Whether exposure of 1,25-dihydroxy vitamin D to the cardiac-specific ANS branches translates into clinical outcomes and reduced cardiovascular risk is not yet clear, but it

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remains an exciting possibility and potential revelation in the long saga that is vitamin D research.

Ultimately, research up to this point has not been executed in a manner that provides definitive evidence of a causal relationship between vitamin D metabolism and cardiovascular risk. Recent insights from the CKD population and the emergence of alternative surrogate markers of cardiovascular risk are opening up further opportunities for long-overdue clarification on this matter. In order to continue to propel the knowledge of this area further, researchers must be cognizant of the large knowledge gap that persists in the literature. As a global scientific community, we must remain diligent in designing and conducting adequate clinical trials that will truly allow us to step into the light and further our understanding of vitamin D and cardiovascular health.

References

- Zittermann A, Prokop S (2014) The role of vitamin D for cardiovascular disease and overall mortality. *Adv Exp Med Biol* 810: 106-19.
- Wang L, Song Y, Manson JE, (2012) Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. *Circ Cardiovasc Qual Outcomes* 5: 819-829.
- Pilz S, Dobnig H, Tomaschitz A, (2012) Low 25-hydroxyvitamin D is associated with increased mortality in female nursing home residents. *J Clin Endocrinol Metab* 97: E653-E657.
- Schneider A, Michos ED (2014) Invited commentary: The association of low vitamin D with cardiovascular disease-getting at the "heart and soul" of the relationship. *Am J Epidemiol* 179: 1288-1290.
- Li Y, Kong J, Qiao G, Uskokovic M, Xiang W, et al. (2004) Vitamin D: a negative endocrine regulator of the renin-angiotensin system and blood pressure. *J Steroid Biochem Mol Biol* 89-90: 387-92.
- Mann MC, Hobbs AJ, Hemmelgarn BR, Roberts DJ, Ahmed SB, et al. (2015) Effect of oral vitamin D analogs on mortality and cardiovascular outcomes among adults with chronic kidney disease: a meta-analysis. *Clin Kidney J* 8: 41-48.
- Ford JA, MacLennan GS, Avenell A, Bolland M, Grey A, et al. (2014) Cardiovascular disease and vitamin D supplementation: trial analysis, systematic review, and meta-analysis. *Am J Clin Nutr* 100: 746-755.
- Palmer SC, McGregor DO, Macaskill P, Craig JC, Elder GJ, et al. (2007) Meta-analysis: vitamin D compounds in chronic kidney disease. *Ann Intern Med* 147: 840-853.
- Go AS, Chertow GM, Fan D (2004) Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 351: 1296-1305.
- Obi Y, Hamano T, Isaka Y (2015) Prevalence and prognostic implications of vitamin D deficiency in chronic kidney disease. *Dis Markers*.
- Saravanan P, Davidson NC (2010) Risk assessment for sudden cardiac death in dialysis patients. *Circ Arryth and Electrophys* 3: 553-559.
- Barron HV, Mesh MD (1996) Autonomic nervous system and sudden cardiac death. *J Am Coll Cardiol* 27: 1053-1060.
- Thayer JF, Yamamoto SS, Brosschot JF (2010) The relationship of autonomic imbalance, heart rate variability, and cardiovascular disease risk factors. *Int J Cardiol* 141: 122-131.
- Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. (1996) Heart Rate Variability: Standards of Measurement, Physiological Interpretation and Clinical Use. *Circulation*. 93: 1043-1065.
- Hayano J, Takahashi H, Toriyama T, Mukai S, Okada A, et al. (1999) Prognostic value of heart rate variability during long-term follow-up in chronic haemodialysis patients with end-stage renal disease. *Nephrol Dial Transplant* 14: 1480-1488.
- Chan CT, Levin NW, Chertow GM, Larive B, Schulman G, et al. (2010) Determinants of cardiac autonomic dysfunction in ESRD. *Clin J Am Soc Nephrol* 5: 1821-1827.
- Mann MC, Exner DV, Hemmelgarn BR, Sola DY, Turin TC, et al. (2013) Vitamin D levels are associated with cardiac autonomic activity in healthy humans. *Nutrients*. 5: 2114-2127.
- Krause R (2013) Vitamin D and UV exposure in chronic kidney disease. *Dermatoendocrinol* 5: 109-116.
- Mann MC, Exner DV, Hemmelgarn BR, Turin TC, Sola DY, et al. (2014) Vitamin D supplementation is associated with improved modulation of cardiac autonomic tone in healthy humans. *Int J Cardiol* 172: 506-508.
- Wolf M, Shah A, Gutierrez O (2007) Vitamin D levels and early mortality among incident hemodialysis patients. *Kidney international* 72: 1004-1013.
- Teng M, Wolf M, Lowrie E, Ofsthun N, Lazarus JM, et al. (2003) Survival of patients under going hemodialysis with paricalcitol or calcitriol therapy. *N Engl J Med* 349: 446-456.
- Mann MC, Exner DV, Hemmelgarn BR, Hanley DA, Turin TC, et al. (2014) The VITAH Trial: Vitamin D supplementation and cardiac autonomic tone in hemodialysis: A blinded, randomized controlled trial (Protocol). *BMC Nephrology* 15: 129.
- Holick MF (2007) Vitamin D Deficiency. *N Eng J Med* 357: 266-281.
- Garcion E, Wion-Barbot N, Montero-Menei CN, Berger F, Wion D (2002) New clues about vitamin D functions in the nervous system. *TRENDS in Endocrinology and Metabolism* 13: 100-105.
- DeLuca GC, Kimball SM, Kolasinski J, Ramagopalan SV, Ebers GC (2013) Review: The role of vitamin D in nervous system health and disease. *Neuropathology and Applied Neurobiology* 39: 458-484.

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