REVIEW ARTICLE

Vitamin D deficiency plays an important role in cardiac disease and affects patient outcome: Still a myth or a fact that needs exploration?

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There is increasing evidence that a low vitamin D status may be an important and hitherto neglected factor of cardiovascular disease. This review is an overview of the current body of literature, and presents evidence of the mechanisms through which vitamin D deficiency affects the cardiovascular system in general and the heart in particular. Available data indicate that the majority of congestive heart failure patients have 25-hydroxyvitamin D deficiency. Furthermore, the low serum 25-hydroxyvitamin D level has a higher impact on hypertension, coronary artery disease an on the occurrence of relevant cardiac events. A serum 25-hydroxyvitamin D level below 75 nmol/l (30 ng/l) is generally regarded as vitamin D insufficiency in both adults and children, while a level below 50 nmol/l (20 ng/l) is considered deficiency. Levels below 50 nmol/l (20 ng/l) are linked independently to cardiovascular morbidity and mortality.

Keywords: Vitamin D deficiency, Congestive heart failure, Coronary artery disease, Cardiovascular outcomes

Contents

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Introduction

Vitamin D deficiency is widely prevalent in the United States and worldwide [1]. Low levels of 25-hydroxy vitamin D [25(OH) D], the principal circulating storage form of vitamin D, are present in one third to one half of otherwise healthy middle-aged to elderly adults [1–3]. Although most consequences of vitamin D deficiency involve the musculoskeletal system, there is a growing body of evidence suggesting that low levels of vitamin D may adversely affect the cardiovascular system [4]. A serum 25-hydroxyvitamin D level below 75 nmol/l (30 ng/l) is generally regarded as vitamin D insufficiency in both adults and children, while a level below 50 nmol/l (20 ng/l) is considered deficiency in both populations [5,6]. Vitamin D deficiency, which is affected by multiple factors (Table 1), appears to have an association with diverse cardiac diseases starting with its direct effect on the cardiac cell, its association with coronary artery disease (CAD), and its risk factors such as diabetes and hypertension (HTN); ending at last and probably not least in its relation with congestive heart failure (CHF). Similarly, there is some evidence that links vitamin deficiency to increased risk of stroke.

This article is an overview of the current data describing the effect of vitamin D on the cardiac cell and the relationship of its deficiency with HTN, CAD, and heart failure. We compare vitamin D to its clinical and laboratory markers as well as to clinical outcomes and cardiac events. Finally, we explore the impact of vitamin D deficiency on cardiovascular outcomes including death, cardiac death, stroke, and myocardial infarction.

Abbreviations

25(OH) D	25-hydroxyvitamin D
CAD	coronary artery disease
HTN	hypertension
CHF	congestive heart failure
VDR	vitamin D receptor
RAAS	renin-angiotensin-aldosterone system
IL	interleukin
TNF	tumor necrosis factor
NYHA	New York Heart Association
NT pro-BNP	N-terminal of the prohormone brain natriuretic peptide
NT-proANP	N-terminal of the prohormone atrial natriuretic peptide
LVEF	left ventricle ejection fraction
LURIC	Ludwigshafen Risk and Cardiovascular Health (LURIC) Study
HR	hazard ratio
OR	Odds Ratio
RR	Relative Ratio

Methods

Relevant studies were identified through electronic searches of MEDLINE and the databases of the Cochrane Central Register of Controlled Trials. The search used the terms ''cardiovascular disorders,'' ''cardiovascular disease,'' ''hypertension,'' ''coronary artery disease,'' or ''congestive heart failure'' paired with ''vitamin D deficiency'' and ''calcitriol''. In addition, we searched bibliographies of relevant studies, reviews and editorial letters between 1990 and 2015 for articles in English. We reviewed the references to identify the studies addressing the role of vitamin D hemostasis in the pathogenesis of cardiovascular disease, and the impact of vitamin D deficiency and supplementation on HTN, CAD, CHF, and cardiovascular outcomes. Although human studies were of interest in regards to outcomes, many animal model studies were included for the purpose of the pathogenesis of vitamin D deficiency role in cardiovascular disease. Out of 3026 articles, 88 were identified as meeting our criteria and were reviewed. Of those 88, 43 were used in the final version of this article.

Table 1. Examples of some causes of vitamin D deficiency or resistance.

Causes of vitamin D deficiency or resistance	
Deficient intake or absorption	Dietary
	Inadequate sunlight exposure
	Malabsorption
	Gastrectomy
	Small bowel disease
	Pancreatic insufficiency
Defective 25-hydroxylation	Liver disease/failure
	Alcoholic cirrhosis
	Anticonvulsants
Loss of vitamin D binding protein	Nephrotic syndrome
Defective 1-alpha 25-hydroxylation	Hypoparathyroidism
	Chronic kidney disease/failure
	1-alpha hydroxylase deficiency (Vitamin D-dependent rickets type 1)
Defective target organ response to calcitriol	Hereditary vitamin D-resistant rickets (Vitamin D-dependent rickets, type 2)