CHAPTER 6

THE ROLE OF VITAMIN D FOR CARDIOVASCULAR DISEASE AND OVERALL MORTALITY

Armin Zittermann* and Sylvana Prokop

Clinic for Thoracic and Cardiovascular Surgery of the Heart and Diabetes Centre, North Rhine-Westphalia, Ruhr University Bochum, Bad Oeynhausen, Germany.

**Corresponding Author: Armin Zittermann—Email: azittermann@hdz-nrw.de*

Abstract: In recent years, it became increasingly clear that vitamin D exerts important pleiotropic effects, besides its well-known effects on extracellular calcium homeostasis and on bone metabolism. This article gives a comprehensive overview of studies on cardiovascular and all-cause mortality with a focus on the most recent data.

25-hydroxyvitamin D (25[OH]D) is the best indicator of vitamin D status. Low 25(OH)D levels are highly prevalent among general populations. Prospective cohort studies support the assumption that poor vitamin D status, e.g., 25(OH) D levels below 30 nmol/l, is independently associated with CVD mortality risk. However, support from randomized controlled trials for a beneficial vitamin D effect on CVD risk is still lacking. Meta-analyses of prospective cohort studies indicate beneficial vitamin D effects on overall mortality as well. There is also likely evidence from meta-analyses of randomized controlled trials that vitamin D may improve overall mortality in elderly people. Therefore, it is reasonable to supplement institutionalized individuals and other people with deficient 25(OH)D levels with daily vitamin D amounts of 20 μg. However, it is also noteworthy that prospective cohort studies provide evidence for an inverse J-shaped association between vitamin D status and overall mortality, indicating increased overall mortality risk not only at deficient 25(OH)D levels but also at 25(OH)D levels above 125 nmol/l. Although there is evidence that high 25(OH)D levels sometimes reflect low availability of the vitamin D hormone 1,25- dihydroxyvitamin D, future studies are still needed to clarify the association of high 25(OH)D levels with high mortality rates more detailed.

Sunlight, Vitamin D and Skin Cancer, Second Edition, edited by Jörg Reichrath.

ABBREVIATIONS

$1,25(OH)_2D$ = 1, 25-dihydroxyvitamin D; 25(OH)D = 25-hydroxyvitamin D; CVD = Cardiovascular Disease; CI = Confidence Interval; HR = Hazard Ratio; ICU = Intensive Care Unit; IU = International Units; KDIGO = Kidney Disease: Improving Global Outcomes; NHANES = National Health and Nutrition Examination Survey; OR = Odds Ratio; PTH = Parathyroid Hormone; RCT = Randomized Clinical Trial; RR = Relative Risk; VITAL = VITamin D and OmegA-3 TriaL; VDR = Vitamin D Receptor; WHI = Women's Health Initiative Study; RECORD = Randomized Evaluation of Calcium OR vitamin D.

INTRODUCTION

Vitamin D is generally known for its pivotal role in extracellular calcium homeostasis and on bone metabolism. In recent years, however, it became increasingly clear that vitamin D has important pleiotropic effects. Together with vitamin D's role on extracellular calcium metabolism these pleiotropic effects may also affect cardiovascular disease (CVD) and all-cause mortality.

Globally, CVD is the number one cause of mortality. In 2005, CVD was responsible for approximately 30% deaths worldwide.[1] Notably, vitamin D deficiency is also very prevalent in general populations. This chapter gives a comprehensive overview of observational and interventional studies on the association between vitamin D and cardiovascular/overall mortality with a focus on the most recent data. When appropriate, results from experimental data are also mentioned.

For this review we performed a systematic literature search in pubmed for relevant publications released until August 31th, 2012. We searched for the following terms: "vitamin D" or "cholecalciferol" or "calcitriol" or "25-hydroxyvitamin D" or "1,25-dihydroxyvitamin D" combined with "cardiovascular disease" or "vascular calcification" or "cardiovascular mortality" or "all-cause mortality" or" overall mortality." Personal collections of articles on this topic as well as references from selected articles were also used to extend the search. Some articles were not cited due to space limitations.

VITAMIN D STATUS IN ADULTS

The best parameter to asses vitamin D status is the serum concentration of 25-hydroxyvitamin D (25[OH]D). Circulating 25(OH)D reflects the sum of oral vitamin D intake from dietary and supplemental sources and of vitamin D synthesis in the skin. The sunlight is responsible for more than 80% of the vitamin D supply. There is evidence that under similar lifestyle conditions geographic latitude is a predictor of vitamin D status, with lower levels in individuals who live farer away from the equator.[2,3] There are also seasonal variations with the highest vitamin D concentrations occurring at the end of summer.[4] Further risk factors for low 25(OH)D levels are older age, female sex, darker skin pigmentation, less sunlight exposure, dietary habits, and absence of vitamin D fortification of foods.[5]

To date, no general agreement has emerged for cut-off levels for a sufficient vitamin D status. Based on the beneficial effects of vitamin D on fracture risk the Institute of Medicine (IOM) has recently stated that 25(OH)D levels below 30 nmol/L and between 30 and 50 nmol/L bear the risk of vitamin D deficiency and inadequacy, respectively.