Some recent abstracts:  

Cardiovascular and Diabetes Issues x Vitamin D  
(plus odds and ends)

J Hypertens. 2010 Jul 5.

Independent associations of serum concentrations of 25-hydroxyvitamin D and parathyroid hormone with blood pressure among US adults. Objective: Vitamin D deficiency or high levels of parathyroid hormone (PTH) appear to be emerging risk factors for hypertension. This study examined whether serum concentrations of 25-hydroxyvitamin D [25(OH)D] and PTH were independently associated with blood pressure and the presence of hypertension or prehypertension among the United States adults. Methods: Cross-sectional data from 7228 participants (aged >/=20 years) in the 2003-2006 National Health and Nutrition Examination Survey were analyzed. The least square means and the regression coefficients of systolic blood pressure, diastolic blood pressure, and pulse pressure across quintiles of serum 25(OH)D and PTH were estimated by conducting multiple linear regression analyses. The adjusted prevalence ratios with 95% confidence intervals for hypertension and prehypertension were estimated using the log-binomial method. Results: Among participants not taking blood pressure medications (n = 5414), the mean age- and sex-adjusted systolic and diastolic blood pressure decreased linearly across quintiles of serum 25(OH)D but increased linearly across quintiles of serum PTH (P < 0.001 for all); these relationships remained significant even after extensively adjusting for covariates. Similarly, across quintiles of serum 25(OH)D, the age-adjusted prevalence of hypertension and the adjusted prevalence ratios for both hypertension and prehypertension decreased linearly (P < 0.001 for all). In contrast, the prevalence of hypertension and prehypertension increased nonlinearly (P < 0.05 for both) and the adjusted prevalence ratios for hypertension increased linearly across quintiles of serum PTH (P < 0.001). Conclusion: Serum concentrations of 25(OH)D and PTH were independently associated with blood pressure and with the presence of hypertension or prehypertension among the United States adults, though casual relationships remain to be elucidated.


OBJECTIVE: To examine whether concentrations of serum 25-hydroxyvitamin D (25[OH]D) and parathyroid hormone (PTH) are associated with surrogate markers of insulin resistance (IR) in U.S. adults without physician-diagnosed diabetes. RESEARCH DESIGN AND METHODS: Cross-sectional data (n = 3,206) from the National Health and Nutrition Examination Survey (NHANES) 2003-2006 were analyzed. RESULTS: The age-adjusted prevalence of hyperinsulinemia, high homeostasis model assessment-IR, high GHb, and fasting and 2-h hyperglycemia decreased linearly across quintiles of 25(OH)D but increased linearly across quintiles of PTH (except for a quadratic trend for fasting hyperglycemia). After extensive adjustment for potential confounders, the relationships between 25(OH)D and the markers of IR and 2-h hyperglycemia decreased linearly across quintiles of 25(OH)D but increased linearly across quintiles of PTH (except for a quadratic trend for fasting hyperglycemia). After extensive adjustment for potential confounders, the relationships between 25(OH)D and the markers of IR and 2-h hyperglycemia persisted. Only hyperinsulinemia was positively associated with PTH (P < 0.05). CONCLUSIONS: Among U.S. adults without physician-diagnosed diabetes, low concentrations of serum 25(OH)D were associated with markers of IR. The role of PTH in IR deserves further investigation.


Vitamin D role and use in prediabetes. OBJECTIVE: To review the role of vitamin D in prediabetes on the basis of evidence from human studies. METHODS: English-language literature in MEDLINE (January 1969-July 2009) was searched for observational studies and randomized controlled trials of vitamin D deficiency and treatment in prediabetes, including impaired fasting glucose, impaired glucose tolerance, and metabolic syndrome. Search terms included hyperglycemia, glucose, glycohemoglobin, insulin resistance, diabetes, homeostasis model assessment, insulin secretion, vitamin D, and related terms. Publications were also identified from review articles and references in the found articles. Abstracts, conference proceedings, case reports, and letters were excluded. Articles concerning only type 1 and type 2 diabetes, hemodialysis, or hyperparathyroidism and studies in children were also excluded. RESULTS: Vitamin D insufficiency is defined by a circulating 25-hydroxyvitamin D
concentration less than 30 ng/mL, and it is prevalent in the United States (77% of the population). Most cross-sectional and prospective studies in various populations show inverse association between circulating 25-hydroxyvitamin D and fasting plasma glucose, impaired glucose tolerance, hemoglobin A1c, metabolic syndrome, and incidence of prediabetes. A few clinical trials suggest beneficial effect of vitamin D supplementation in prediabetes, including improved insulin secretion, basal fasting insulin sensitivity, and postprandial peripheral insulin resistance. The limitations of the studies are small sample size, short duration of follow-up, lack of control groups, and inability to achieve vitamin D sufficiency with treatment. **CONCLUSION:** Available data suggest that achieving vitamin D sufficiency may be beneficial in patients with prediabetes, although clinical trials are needed to provide evidence-based recommendations.


**Does vitamin D deficiency cause hypertension? Current evidence from clinical studies and potential mechanisms.** Vitamin D deficiency is widely prevalent across all ages, races, geographical regions, and socioeconomic strata. In addition to its important role in skeletal development and calcium homeostasis, several recent studies suggest its association with diabetes, hypertension, cardiovascular disease, certain types of malignancy, and immunologic dysfunction. Here, we review the current evidence regarding an association between vitamin D deficiency and hypertension in clinical and epidemiological studies. We also look into plausible biological explanations for such an association with the renin-angiotensin-aldosterone system and insulin resistance playing potential roles. Taken together, it appears that more studies in more homogeneous study populations are needed before a firm conclusion can be reached as to whether vitamin D deficiency causes or aggravates hypertension and whether vitamin D supplementation is safe and exerts cardioprotective effects. The potential problems with bias and confounding factors present in previous epidemiological studies may be overcome or minimized by well designed randomized controlled trials in the future.


**The Effects of Vitamin D Therapy on Left Ventricular Structure and Function - Are These the Underlying Explanations for Improved CKD Patient Survival?** Cardiovascular disease is a major cause of death among patients with chronic kidney disease and vitamin D deficiency is a common problem also among these patients. Abnormalities in left ventricular size and function are frequent, as they are encountered in 70-80% of incident dialysis patients. These alterations develop early in the course of renal disease and their prevalence progresses in parallel with the decline in renal function. This process of left ventricular dilatation with compensatory hypertrophy continues after the institution of dialysis therapy, especially in the first year. The main factors responsible for the progression of left ventricular hypertrophy (LVH) are considered to be blood pressure and anemia, and in patients receiving hemodialysis, the arteriovenous fistula, volume overload and abnormalities in mineral metabolism. This additional potential set of factors related to LVH - mineral and bone metabolism - is intriguing and begs an immediate question: by what possible mechanism can these factors be linked to cardiac morphology? Recent observational studies have indeed indicated that vitamin D treatment was associated with a significant reduction of cardiovascular death among dialysis patients, and a reduction in LVH; in contrast, other studies suggested that excess vitamin D contributes to risk of hypercalcemia and vascular calcification, which is associated with reduced survival and morbidity. **This review examines the evidence linking vitamin D with cardiac structure and function.**

**Diabetes Care.** 2010 Jul 6.

**Vitamin D levels and mortality in type 2 diabetes.** Abstract. Objective. To evaluate vitamin D as predictor of all-cause and cardiovascular mortality and risk of progression to micro- or macroalbuminuria in type 2 diabetic patients. Research Design and Methods In a longitudinal observational follow-up study, 289 type 2 diabetic patients with normoalbuminuria (n=172), microalbuminuria (n=73) and macroalbuminuria (n=44) at baseline, were followed for a median (range) of 15.0 (0.2-23) years. Mean (SD) age was 54(9) years. Plasma 25-hydroxyvitamin D(3), 25(OH)D(3) levels were determined by high performance liquid chromatography/tandem mass spectrometry on baseline samples. Severe vitamin D deficiency was defined as the lower 10% percentile (<13.9 nmol/l). Results. Median (range) vitamin D level was 35.7 (5-136.7) nmol/l. Vitamin D levels were not associated with age, sex, estimated glomerular filtration rate (eGFR), urinary albumin excretion rate (UAER) or HbA1c at baseline, but low levels were weakly associated with elevated systolic blood pressure (R=0.13, p=0.03). During follow-up, 196 (68%) patients died. All-cause mortality was increased in patients with severe vitamin D deficiency; HR [95% CI] 1.96 [1.29-2.98]. The association persisted after adjustment for UAER, HbA1c, diabetes duration and conventional...
cardiovascular risk factors; HR 2.03 [1.31-3.13]. Severe vitamin D deficiency was associated with increased cardiovascular mortality; HR 1.95 [1.11-3.44]. The association persisted after adjustment; HR 1.90 [1.15-3.10]. Severe vitamin D deficiency at baseline did not predict progression to micro- or macroalbuminuria.

**Conclusions.** In type 2 diabetic patients, severe vitamin D deficiency predicts increased risk of all-cause and cardiovascular mortality, independent of UAER and conventional cardiovascular risk factors. Whether vitamin D substitution improves prognosis remains to be investigated.


**The impact of vitamin D deficiency on diabetes and cardiovascular risk.** PURPOSE OF REVIEW: To review the association between vitamin D deficiency and diabetes and cardiovascular risk. RECENT FINDINGS: Vitamin D deficiency is newly recognized as a common condition of increasing prevalence worldwide. Clinically, vitamin D has an established role in calcium and bone metabolism and has recently been shown to be associated with increased risk of developing type 1 and type 2 diabetes mellitus and cardiovascular disease (CVD), as well as with cardiovascular risk factors such as hypertension and obesity. The molecular mechanisms of these associations remain incompletely understood. The active metabolite of vitamin D regulates transcription of multiple gene products with antiproliferative, prodifferentiative, and immunomodulatory effects. Although vitamin D deficiency is frequently unrecognized clinically, laboratory measurement is easy to perform and treatment of vitamin D deficiency is relatively well tolerated and inexpensive. Limited, yet promising, results of proof-of-concept intervention studies of using vitamin D in diabetes will be presented. SUMMARY: The high prevalence of vitamin D deficiency and plausible molecular mechanisms linking this to diabetes and cardiovascular risk suggest treatment of vitamin D deficiency to prevent and/or treat diabetes is a promising field to explore.


**Predicted 25-hydroxyvitamin D score and incident type 2 diabetes in the Framingham Offspring Study.** BACKGROUND: Accumulating evidence suggests that vitamin D is involved in the development of type 2 diabetes (T2D). OBJECTIVE: Our objective was to examine the relation between vitamin D status and incidence of T2D. DESIGN: We used a subsample of 1972 Framingham Offspring Study participants to develop a regression model to predict plasma 25-hydroxyvitamin D [25(OH)D] concentrations from age, sex, body mass index, month of blood sampling, total vitamin D intake, smoking status, and total energy intake. Using this model, we calculated the predicted 25(OH)D score for each nondiabetic participant at the cohort's fifth examination to assess the association between the predicted 25(OH)D score and incidence of T2D by using Cox proportional hazards models. RESULTS: A total of 133 T2D cases were identified over a 7-y average follow-up. In comparison with individuals in the lowest tertile of the predicted 25(OH)D score at baseline, those in the highest tertile had a 40% lower incidence of T2D after adjustment for age, sex, waist circumference, parental history of T2D, hypertension, low HDL cholesterol, elevated triglycerides, impaired fasting glucose, and Dietary Guidelines for Americans Adherence Index score (hazard ratio: 0.60; 95% CI: 0.37, 0.97; P for trend = 0.03). CONCLUSIONS: Our findings suggest that higher vitamin D status is associated with decreased risk of T2D. Maintaining optimal 25(OH)D status may be a strategy to prevent the development of T2D.

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**Cardiac structure and diastolic function in mild primary hyperparathyroidism.** CONTEXT: Data on the presence, extent, and reversibility of cardiovascular disease in primary hyperparathyroidism (PHPT) are conflicting. OBJECTIVE: To evaluate the heart in PHPT, we assessed cardiac structure and diastolic function in patients with mild PHPT compared with age- and sex-matched controls. DESIGN: This was a case-control study. SETTINGS: The study was conducted in a university hospital Metabolic Bone Diseases Unit. PARTICIPANTS: Fifty-four men and women with PHPT and 76 controls without PHPT participated in the study. OUTCOME MEASURES: We measured left ventricular mass index (LVMI), the presence of mitral annular calcification, the ratio of early to late diastolic mitral inflow velocities (E/A), and early diastolic velocity of the lateral mitral annulus using Doppler tissue imaging (tissue Doppler e'). RESULTS: Patients had mild disease with mean (+/-sd) serum calcium 10.5 +/- 0.5 mg/dl and PTH 96 +/- 45 pg/ml. LVMI and diastolic function were normal in PHPT. There was no difference in LVMI (98 +/- 23 vs. 96 +/- 24 g/m(2), P = 0.69) or the frequency of mitral annular calcification between PHPT cases and controls. Diastolic function variables (E/A and tissue Doppler e') were higher (better) in cases compared with controls, although both were within the reference range. PHPT patients with low E/A had higher serum PTH (121 +/- 36 vs. 89 +/- 46 pg/ml, P = 0.03) and calcium (10.8 +/- 0.4 vs. 10.5 +/- 0.5 mg/dl, P = 0.05) than those with normal values. Finally, we found LVMI to be inversely associated with serum 25-
hydroxyvitamin D in PHPT ($r = -0.29$, $P < 0.05$). All findings persisted after adjustment for group differences in cardiovascular risk factors. CONCLUSIONS: Patients with biochemically mild PHPT do not have evidence of increased left ventricular mass, diastolic dysfunction, or increased valvular calcifications. However, the data support an association between low vitamin D levels and the development of left ventricular hypertrophy in this disorder. Finally, the increased serum calcium and PTH levels in those with diastolic dysfunction suggest that disease severity may determine the presence of cardiac manifestations in PHPT.

Current Opinion in Endocrinology, Diabetes & Obesity. 17(2):113-9, 2010 Apr. The impact of vitamin D deficiency on diabetes and cardiovascular risk. PURPOSE OF REVIEW: To review the association between vitamin D deficiency and diabetes and cardiovascular risk. RECENT FINDINGS: Vitamin D deficiency is newly recognized as a common condition of increasing prevalence worldwide. Clinically, vitamin D has an established role in calcium and bone metabolism and has recently been shown to be associated with increased risk of developing type 1 and type 2 diabetes mellitus and cardiovascular disease (CVD), as well as with cardiovascular risk factors such as hypertension and obesity. The molecular mechanisms of these associations remain incompletely understood. The active metabolite of vitamin D regulates transcription of multiple gene products with antiproliferative, prodifferentiative, and immunomodulatory effects. Although vitamin D deficiency is frequently unrecognized clinically, laboratory measurement is easy to perform and treatment of vitamin D deficiency is relatively well tolerated and inexpensive. Limited, yet promising, results of proof-of-concept intervention studies of using vitamin D in diabetes will be presented. SUMMARY: The high prevalence of vitamin D deficiency and plausible molecular mechanisms linking this to diabetes and cardiovascular risk suggest treatment of vitamin D deficiency to prevent and/or treat diabetes is a promising field to explore.

Nephrology Dialysis Transplantation. 25(2):503-9, 2010 Feb. Association of low serum 25-hydroxyvitamin D levels and high arterial blood pressure in the elderly. BACKGROUND: Vitamin D and calcium metabolism are involved in vascular smooth muscle cell proliferation, endothelial function and blood pressure (BP) regulation. Their physiopathology has been a matter of intensive clinical investigation with variable and sometimes contradictory results. Vitamin D insufficiency is highly prevalent in the general population, particularly among the elderly. We evaluated the association between serum 25(OH)-D levels and arterial BP in this population. METHODS: An epidemiological cross-sectional study was designed to analyse the prevalence of hypovitaminosis D ('D'AVIS' study) in our reference area. The study was performed on a representative random sample of the population over 64 years of age obtained from five primary health care areas. A medical record, arterial BP and biological analysis: serum 25(OH)-D, iPTH, creatinine, urea, calcium, albumin were obtained. RESULTS: A total of 237 subjects (53% women), aged between 64 and 93 (mean 71.7 +/- 5.3), were evaluated. The mean serum 25(OH)-D levels were 17.21 +/- 7.57 ng/ml (interval 5-54; 86% had <25 ng/ml). The mean BP was 138.8 +/- 14/80 +/- 7.4 mmHg, and 46% were on antihypertensive treatment. A significant negative association was observed between serum 25(OH)-D levels and systolic BP ($r = -0.153$, $P = 0.018$) and diastolic BP ($r = -0.152$, $P = 0.019$). This association persisted after controlling for possible confounders in the multivariate analyses. CONCLUSIONS: Low serum 25(OH)-D levels were inversely and independently associated with BP. Supplemental measures to prevent hypovitaminosis D in this population would be important, not only to protect the skeletal system but also for the possible beneficial effects on the cardiovascular system and the BP regulation.

Neurology. 74(1):27-32, 2010 Jan 5. Association of vitamin D deficiency with cognitive impairment in older women: cross-sectional study. OBJECTIVE: The association between low serum 25-hydroxyvitamin D [25(OH)D] concentration and cognitive decline has been investigated by only a few studies, with mixed results. The objective of this cross-sectional population-based study was to examine the association between serum 25(OH)D deficiency and cognitive impairment while taking confounders into account. METHODS: The subjects, 752 women aged $> or =75$ years from the Epidemiologie de l'Osteoporose (EPIDOS) cohort, were divided into 2 groups according to serum 25(OH)D concentrations (either deficient, <10 ng/mL, or nondeficient, $> or =10$ ng/mL). Cognitive impairment was defined as a Pfeiffer Short Portable Mental State Questionnaire (SPMSQ) score <8. Age, body mass index, number of chronic diseases, hypertension, depression, use of psychoactive drugs, education level, regular physical activity, and serum intact parathyroid hormone and calcium were used as potential confounders. RESULTS: Compared with women with serum 25(OH)D concentrations $> or =10$ ng/mL ($n = 623$), the women with 25(OH)D deficiency ($n = 129$) had a lower mean SPMSQ score ($p < 0.001$) and more often had an SPMSQ score <8 ($p = 0.006$). There was no
significant linear association between serum 25(OH)D concentration and SPMSQ score (beta = -0.003, 95% confidence interval -0.012 to 0.006, p = 0.512). However, serum 25(OH)D deficiency was associated with cognitive impairment (crude odds ratio OR = 2.08 with p = 0.007; adjusted OR = 1.99 with p = 0.017 for full model; and adjusted OR = 2.03 with p = 0.012 for stepwise backward model). CONCLUSIONS: 25-Hydroxyvitamin D deficiency was associated with cognitive impairment in this cohort of community-dwelling older women.


Serum 25-hydroxyvitamin D levels are strongly related to systolic blood pressure but do not predict future hypertension. This is a mini-review of vitamin D(3), its active metabolites and their functioning in the central nervous system (CNS), especially in relation to nervous system pathologies and aging. The vitamin D(3) endocrine system consists of 3 active calcipherol hormones: calcidiol (25OHD(3)), 1alpha-calcitriol (1alpha,25(OH)2D(3)) and 24-calcitriol (24,25(OH)2D(3)). The impact of the calcipherol hormone system on aging, health and disease is discussed. Low serum calcidiol concentrations are associated with an increased risk of severe chronic diseases including osteoporosis, cancer, diabetes, autoimmune disorders, hypertension, atherosclerosis and muscle weakness all of which can be considered aging-related diseases. The relationship of many of these diseases and aging-related changes in physiology show a U-shaped response curve to serum calcidiol concentrations. Clinical data suggest that vitamin D(3) insufficiency is associated with an increased risk of several CNS diseases, including multiple sclerosis, Alzheimer's and Parkinson's disease, seasonal affective disorder and schizophrenia. In line with this, recent animal and human studies suggest that vitamin D insufficiency is associated with abnormal development and functioning of the CNS. Overall, imbalances in the calcipherol system appear to cause abnormal function, including premature aging, of the CNS.


Health effects of vitamin D. Increasing data suggest that many or most adults in the United States and Europe would benefit from vitamin D supplements. This review summarizes the benefits of vitamin D with the strongest evidence today from randomized controlled trials for fall and fracture prevention. Beyond fall and fracture prevention, vitamin D may also reduce overall morbidity by multiple mechanisms. Prospective epidemiological studies supported by strong mechanistic evidence suggest a reduction of cardiovascular disease (incident hypertension and cardiovascular mortality) and colorectal cancer, extending to weaker evidence on immune-modulatory and anti-inflammatory benefits of vitamin D.


Does vitamin D modulate asymmetric dimethylarginine and C-reactive protein concentrations? BACKGROUND: Vitamin D deficiency is associated with significant increases in the incidence of cardiovascular risk factors and mortality. However, the mechanisms underlying this association remain unclear. The current study evaluated the possible relationships among vitamin D status, endothelial dysfunction, and inflammation. METHODS: Plasma concentrations of 25-hydroxyvitamin D(3) were determined by radioimmunoassay in a normal population cohort (n=253) aged 51 to 77 years (mean 63.4+/-.6 years). Asymmetric dimethylarginine, a marker/mediator of endothelial dysfunction, was assayed by high-performance liquid chromatography. High-sensitivity C-reactive protein levels were used as a marker of inflammatory activation. RESULTS: On univariate analyses, low 25-hydroxyvitamin D(3) levels were inversely correlated with asymmetric dimethylarginine concentrations, high-sensitivity C-reactive protein levels, and body mass index. Seasonal fluctuations in 25-hydroxyvitamin D(3) levels were associated with reciprocal asymmetric dimethylarginine concentration fluctuations. Hypertension and treatment with an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker also were associated with low 25-hydroxyvitamin D(3) levels. On multiple linear analysis, both asymmetric dimethylarginine (beta=-0.19, P=.003) and high-sensitivity C-reactive protein (beta=-0.14, P=.03) concentrations were inversely correlated with plasma 25-hydroxyvitamin D(3) concentrations; other significant correlates were male gender (beta=0.19, P=.003), calcium levels (beta=0.14, P=.03), and use of angiotensin-converting enzyme inhibitor (beta=-0.17, P=.007). CONCLUSION: Low 25-hydroxyvitamin D(3) levels are associated with markers of endothelial dysfunction and inflammatory activation, representing potential mechanisms for incremental coronary risk.

**Vitamin D: in the evolution of human skin colour.** The natural selection hypothesis suggests that lighter skin colour evolved to optimise vitamin D production. Some authors question if vitamin D deficiency leads to sufficient health problems to act as a selection pressure. This paper reviews the numerous effects of vitamin D deficiency on human health and argues that vitamin D deficiency is sufficient to pose as a potent selection pressure for lighter skin colour. Vitamin D deficiency manifesting as rickets and osteomalacia are sufficient to impair reproductive success, but additionally, animal studies and some clinical observations suggest that vitamin D may have more direct impact on human fertility. **Vitamin D deficiency may lead to a whole host of clinical conditions which impair health and increase mortality rates: increase susceptibility to bacterial and viral infections; rickets, osteomalacia and osteoporosis, with increased risk of falls and fractures; increased risk of cancers; hypertension and cardiovascular disease; maturity onset diabetes; autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease and Type 1 diabetes; and gum disease.** We submit that at higher latitudes, lighter skin colour evolved to facilitate vitamin D production under conditions of low ultra-violet B radiation in order to avoid a plethora of ill health, reproductive difficulties and early mortality.


**Role of vitamin d in insulin secretion and insulin sensitivity for glucose homeostasis.** Vitamin D functions are not limited to skeletal health benefits and may extend to preservation of insulin secretion and insulin sensitivity. This review summarizes the literature related to potential vitamin D influences on glucose homeostasis and insulin sensitivity. Cross-sectional data provide some evidence that circulating 25-hydroxyvitamin D (25(OH)D) is inversely associated with insulin resistance, although direct measurements of insulin sensitivity are required for confirmation. Reported associations with insulin secretion, however, are contradictory. **Available prospective studies support a protective influence of high 25(OH)D concentrations on type 2 diabetes mellitus risk.** There is a general lack of consistency in vitamin D intervention outcomes on insulin secretion and sensitivity, likely due to differences in subject populations, length of interventions, and forms of vitamin D supplementation. Vitamin D receptor gene polymorphisms and vitamin D interactions with the insulin like growth factor system may further influence glucose homeostasis. The ambiguity of optimal vitamin D dosing regimens and optimal therapeutic concentrations of serum 25(OH)D limit available intervention studies. Future studies, including cross-sectional and prospective, should be performed in populations at high risk for both vitamin D deficiency and type 2 diabetes mellitus. Well-designed, placebo-controlled, randomized intervention studies are required to establish a true protective influence of vitamin D on glucose homeostasis.


**Adiposity, cardiometabolic risk, and vitamin D status: the Framingham Heart Study.** OBJECTIVE: Because vitamin D deficiency is associated with a variety of chronic diseases, understanding the characteristics that promote vitamin D deficiency in otherwise healthy adults could have important clinical implications. Few studies relating vitamin D deficiency to obesity have included direct measures of adiposity. Furthermore, the degree to which vitamin D is associated with metabolic traits after adjusting for adiposity measures is unclear. RESEARCH DESIGN AND METHODS: We investigated the relations of serum 25-hydroxyvitamin D (25[OH]D) concentrations with indexes of cardiometabolic risk in 3,890 nondiabetic individuals; 1,882 had subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) volumes measured by multidetector computed tomography (CT). RESULTS: In multivariable-adjusted regression models, 25(OH)D was inversely associated with winter season, waist circumference, and serum insulin (P < 0.005 for all). In models further adjusted for CT measures, 25(OH)D was inversely related to SAT (-1.1 ng/ml per SD increment in SAT, P = 0.016) and VAT (-2.3 ng/ml per SD, P < 0.0001). The association of 25(OH)D with insulin resistance measures became nonsignificant after adjustment for VAT. Higher adiposity volumes were correlated with lower 25(OH)D across different categories of BMI, including in lean individuals (BMI <25 kg/m(2)). The prevalence of vitamin D deficiency (25[OH]D <20 ng/ml) was threefold higher in those with high SAT and high VAT than in those with low SAT and low VAT (P < 0.0001). CONCLUSIONS: Vitamin D status is strongly associated with variation in subcutaneous and especially visceral adiposity. The mechanisms by which adiposity promotes vitamin D deficiency warrant further study.


**Hypovitaminosis D: a new risk marker for cardiovascular disease.**
**Vitamin D deficiency and risk for cardiovascular disease.** Vitamin D is an important prohormone for optimal intestinal calcium absorption for mineralization of bone. Because the vitamin D receptor is present in multiple tissues, there has been interest in evaluating other potential functions of vitamin D, particularly, in cardiovascular diseases (CVD). Cross-sectional studies have reported that vitamin D deficiency is associated with increased risk of CVD, including hypertension, heart failure, and ischemic heart disease. Initial prospective studies have also demonstrated that vitamin D deficiency increases the risk of developing incident hypertension or sudden cardiac death in individuals with preexisting CVD. Very few prospective clinical studies have been conducted to examine the effect of vitamin D supplementation on cardiovascular outcomes. The mechanism for how vitamin D may improve CVD outcomes remains obscure; however, potential hypotheses include the downregulation of the renin-angiotensin-aldosterone system, direct effects on the heart, and vasculature or improvement of glycemic control. This review will examine the epidemiologic and clinical evidence for vitamin D deficiency as a cardiovascular risk factor and explore potential mechanisms for the cardioprotective effect of vitamin D.

**Vitamin D and cardiovascular disease.** Cardiovascular disease (CVD) is a major cause of morbidity and mortality worldwide. Recently vitamin D deficiency has been identified as a potential risk factor for many diseases not traditionally associated with vitamin D, such as cancer and CVD. This review discusses the evidence suggesting an association between low 25-hydroxyvitamin D levels and CVD and the possible mechanisms mediating it. Vitamin D deficiency has been associated with CVD risk factors such as hypertension and diabetes mellitus, with markers of subclinical atherosclerosis such as intima-media thickness and coronary calcification as well as with cardiovascular events such as myocardial infarction and stroke as well as congestive heart failure. It could be suggested that vitamin D deficiency contributes to the development of CVD through its association with risk factors, such as diabetes and hypertension. However, direct effects of vitamin D on the cardiovascular system may also be involved. Vitamin D receptors are expressed in a variety of tissues, including cardiomyocytes, vascular smooth muscle cells and endothelial cells and vitamin D has been shown to affect inflammation and cell proliferation and differentiation. While much evidence supports a potential antiatherosclerotic effect of vitamin D, prospective, placebo-controlled randomized as well as mechanistic studies are needed to confirm this association. Since vitamin D deficiency is easy to screen for and treat, the confirmation of such an association could have important implications for both, patient care and health policy.

**Plasma 25-hydroxyvitamin d is associated with markers of the insulin resistant phenotype in nondiabetic adults.** We examined the cross-sectional association between plasma 25-hydroxyvitamin D [25(OH)D] and markers of the insulin resistant phenotype. Plasma 25(OH)D concentrations were measured in 808 nondiabetic participants of the Framingham Offspring Study. Outcome measures included fasting and 2-h post 75-g oral glucose tolerance test (OGTT) glucose and insulin; these were used to calculate the homeostatic model assessment-insulin resistance (HOMA-IR) and insulin sensitivity index (ISI(0,120)). We also measured plasma adiponectin, triacylglycerol, and HDL cholesterol concentrations as markers of the insulin-resistant phenotype. After adjusting for age, sex, BMI, waist circumference, and current smoking status, plasma 25(OH)D concentration was inversely associated with fasting plasma glucose and insulin concentrations, and HOMA-IR. Compared with the participants in the lowest tertile category of plasma 25(OH)D, those in the highest tertile category had a 1.6% lower concentration of fasting plasma glucose (P-trend = 0.007), 9.8% lower concentration of fasting plasma insulin (P-trend = 0.001), and 12.7% lower HOMA-IR score (P-trend < 0.001). After adjusting for age and sex, plasma 25(OH)D was positively associated with ISI(0,120), plasma adiponectin, and HDL cholesterol and inversely associated with plasma triacylglycerol, but these associations were no longer significant after further adjustment for BMI, waist circumference, and current smoking status. 25(OH)D and 2-h post-OGTT glucose were not associated. Among adults without diabetes, vitamin D status was inversely associated with surrogate fasting measures of insulin resistance. These results suggest that vitamin D status may be an important determinant for type 2 diabetes mellitus. hyperglycemia persisted. Only hyperinsulinemia was positively associated with PTH (P < 0.05). CONCLUSIONS: Among U.S. adults without physician-diagnosed diabetes, low concentrations of serum 25(OH)D were associated with markers of IR. The role of PTH in IR deserves further investigation.
Skin cancer prevention and UV-protection: how to avoid vitamin D-deficiency? Because solar UV-radiation represents the most important environmental risk factor for the development of non-melanoma skin cancer, UV protection is important to prevent these malignancies. Consequently, public health campaigns were developed to improve the knowledge of the general population regarding the role of UV-radiation for the development of skin cancer. However, it has to be noted that vitamin D-mediated positive effects of UV light were not adequately considered in most of these campaigns, that often propose a strict ‘no sun policy’ without giving recommendations how to prevent vitamin D-deficiency. Under our living conditions, approximately 90% of all vitamin D needed by the human body has to be formed in the skin through the action of UV-B-radiation and it has been shown that strict sun protection causes vitamin D-deficiency. This dilemma represents a serious problem, for an association of vitamin D-deficiency and multiple independent diseases including various types of cancer, bone diseases, autoimmune diseases, infectious diseases, cardiovascular diseases and hypertension has now been reported in a large number of laboratory and epidemiologic investigations. Although further work is necessary to define an adequate vitamin D-status and adequate guidelines for UV-exposure, it is at present mandatory that guidelines for UV-exposure (e.g. in skin cancer prevention campaigns) consider these facts and give recommendations how to prevent vitamin D-deficiency. At present, most experts in the field agree that the evidence to date suggests that daily intake of 1000-2000 IU vitamin D could reduce the incidence of vitamin D-deficiency-related diseases with minimal risk in Europe, the US, and other countries. In this review, we analyze the present literature to help developing well-balanced guidelines on UV-protection that ensure an adequate vitamin D-status. These recommendations will hopefully protect us against vitamin D-deficiency without increasing the risk to develop UV-induced skin cancer.

Vitamin D and calcium insufficiency-related chronic diseases: molecular and cellular pathophysiology. A compromised vitamin D status, characterized by low 25-hydroxyvitamin D (25-(OH)D) serum levels, and a nutritional calcium deficit are widely encountered in European and North American countries, independent of age or gender. Both conditions are linked to the pathogenesis of many degenerative, malignant, inflammatory and metabolic diseases. Studies on tissue-specific expression and activity of vitamin D metabolizing enzymes, 25-(OH)D-1 alpha-hydroxylase and 25-(OH)D-24-hydroxylase, and of the extracellular calcium-sensing receptor (CaR) have led to the understanding of how, in non-renal tissues and cellular systems, locally produced 1,25-dihydroxyvitamin D(3) (1,25-(OH)(2)D(3)) and extracellular Ca(2+) act jointly as key regulators of cellular proliferation, differentiation and function. Impairment of cooperative signalling from the 1,25-(OH)(2)D(3)-activated vitamin D receptor (VDR) and from the CaR in vitamin D and calcium insufficiency causes cellular dysfunction in many organs and biological systems, and, therefore, increases the risk of diseases, particularly of osteoporosis, colorectal and breast cancer, inflammatory bowel disease, insulin-dependent diabetes mellitus type I, metabolic syndrome, diabetes mellitus type II, hypertension and cardiovascular disease. Understanding the underlying molecular and cellular processes provides a rationale for advocating adequate intake of vitamin D and calcium in all populations, thereby preventing many chronic diseases worldwide.


Serum vitamin D, parathyroid hormone levels, and carotid atherosclerosis. Evidence suggests low vitamin D and elevated parathyroid hormone (PTH) concentrations may increase risk for cardiovascular disease. However, little is known about the association between vitamin D or PTH and subclinical atherosclerosis. This cross-sectional study included 654 community-dwelling older adults aged 55-96 years (mean age, 75.5 years) without a history of coronary heart disease, revascularization, or stroke enrolled in the Rancho Bernardo Study who completed a clinic examination in 1997-1999 and provided a blood sample for determination of serum 25-hydroxyvitamin D [25(OH)D], 1,25-dihydroxyvitamin D [1,25(OH)(2)D], and PTH concentrations. Carotid artery intima-media wall thickness (IMT) was measured as an indicator of atherosclerosis at two sites with B-mode ultrasound. After adjusting for age, sex, smoking, alcohol intake, waist-to-hip ratio, exercise, season of blood draw, diabetes, and hypertension, geometric mean internal carotid IMT (p(trend) 0.022), but not common carotid IMT (p(trend) 0.834) decreased in a dose-dependent fashion with increasing concentration of 25(OH)D. There was no association of 1,25(OH)(2)D or PTH with either measure of carotid IMT. In subgroup analyses, 1,25(OH)(2)D was inversely associated with internal carotid IMT among those with hypertension (p for interaction 0.036). These findings from a population-based cohort of older adults suggest a potential role for vitamin D in the development of subclinical atherosclerosis. Additional research is needed to determine whether vitamin D
may influence the progression of atherosclerosis, including the effects of supplementation on the atherosclerotic process.

**Is vitamin D the fountain of youth?** OBJECTIVE: To review the role of vitamin D deficiency for both classic and "nonclassic" effects and raise the caution that association does not prove causation. METHODS: The pertinent literature regarding vitamin D and its effects on bone, muscle function, immune function, glucose tolerance, cancer risk, and development of cardiovascular disease and other conditions is reviewed. In addition, the limitations of observational studies are discussed. RESULTS: Vitamin D inadequacy is common worldwide and classically causes osteomalacia and rickets. More recently, the contribution of low vitamin D status to increased falls and fracture risk has become appreciated. Additionally, nonclassic effects of vitamin D inadequacy are being recognized, and low vitamin D status is being potentially associated with a multitude of conditions (including Alzheimer disease, osteoarthritis, multiple sclerosis, and hypertension) and higher overall mortality. It is important to recognize that associations in observational studies can be due to chance, bias, or confounders or may be indicative of causality. CONCLUSION: Because vitamin D deficiency has been established to have adverse musculoskeletal consequences, optimization of vitamin D status, for both the individual patient and the overall population, is indicated.

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**Genetic variation in CYP27B1 is associated with congestive heart failure in patients with hypertension.** AIMS: We tested the hypothesis that genetic variation in vitamin D-dependent signaling is associated with congestive heart failure in human subjects with hypertension. MATERIALS & METHODS: Functional polymorphisms were selected from five candidate genes: CYP27B1, CYP24A1, VDR, REN and ACE. Using the Marshfield Clinic Personalized Medicine Research Project, we genotyped 205 subjects with hypertension and congestive heart failure, 206 subjects with hypertension alone and 206 controls (frequency matched by age and gender). RESULTS: In the context of hypertension, a SNP in CYP27B1 was associated with congestive heart failure (odds ratio: 2.14 for subjects homozygous for the C allele; 95% CI: 1.05-4.39). CONCLUSION: Genetic variation in vitamin D biosynthesis is associated with increased risk of heart failure.

**The association of vitamin D deficiency and insufficiency with diabetic nephropathy: implications for health disparities.** OBJECTIVE: To evaluate the association between vitamin D deficiency and insufficiency with diabetic nephropathy across racial/ethnic groups. METHODS: Cross-sectional analysis of the 2001 to 2006 National Health and Nutrition Examination Survey. A nationally representative sample of 1216 adults (> =20 years old) with diagnosed diabetes provides population estimates for >12.6 million individuals. Nephropathy was defined as urinary albumin-to-creatinine ratio > =30 mg/g in a random spot urine sample. Serum 25-hydroxycalciferol vitamin D levels were characterized as <20 ng/mL vitamin D deficiency, 20 to 29 ng/mL vitamin D insufficiency, and > =30 ng/mL normal vitamin D. RESULTS: Overall, 30.7% of adults with diabetes have nephropathy, 48.9% have vitamin D deficiency and 36.6% have vitamin D insufficiency. Minorities are more likely to have nephropathy (non-Hispanic whites, 27.8%; non-Hispanic blacks, 36.2%; Hispanics 38.5%; P = .02) and vitamin D deficiency (non-Hispanic whites, 39.5%; non-Hispanic blacks, 80.4%; Hispanic, 59.0%; P < .01). Higher proportions of individuals with nephropathy have vitamin D deficiency than individuals without nephropathy (53.2% vs 47.0%; P = .03). Logistic regressions demonstrate vitamin D deficiency and insufficiency are associated with the presence of nephropathy after adjustment for race/ethnicity, age, sex, hypertension, high cholesterol, smoking status, and use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (odds ratio, 1.85; 95% CI, 1.06-3.23 for vitamin D deficiency; and CONCLUSIONS: There is a high prevalence of vitamin D deficiency and insufficiency in individuals with diabetes; minorities have the highest prevalences. Thus, evaluating vitamin D levels in people with diabetes may be warranted. There is an independent association between vitamin D deficiency and vitamin D insufficiency with the presence of nephropathy, even after adjustment for race/ethnicity and other variables. Further studies of this relationship may lead to new interventions that decrease health disparities in the progression of diabetic nephropathy.
Vitamin D and mortality in older men and women. OBJECTIVE: Vitamin D deficiency is common among the elderly and may contribute to cardiovascular disease. The aim of our study was to elucidate whether low serum levels of 25-hydroxyvitamin D [25(OH)D] are associated with an increased risk of all-cause and cardiovascular mortality. DESIGN AND PATIENTS: The Hoorn Study is a prospective population-based study among older men and women. MEASUREMENTS: Fasting serum 25(OH)D was determined in 614 study participants at the follow-up visit in 2000-2001, the baseline for the present analysis. To account for sex differences and seasonal variations of 25(OH)D levels we formed sex-specific quartiles, which were calculated from the 25(OH)D values of each season. RESULTS: After a mean follow-up period of 6.2 years, 51 study participants died including 20 deaths due to cardiovascular causes. Unadjusted Cox proportional hazard ratios (HRs; with 95% confidence intervals) for all-cause and cardiovascular mortality in the first when compared with the upper three 25(OH)D quartiles were 2.24 (1.28-3.92; P = 0.005) and 4.78 (1.95-11.69; P = 0.001), respectively. After adjustment for age, sex, diabetes mellitus, smoking status, arterial hypertension, high-density lipoprotein-cholesterol, glomerular filtration rate and waist-to-hip ratio, the HRs remained significant for all-cause [1.97 (1.08-3.58; P = 0.027)] and for cardiovascular mortality [5.38 (2.02-14.34; P = 0.001)]. CONCLUSIONS: Low 25(OH)D levels are associated with all-cause mortality and even more pronounced with cardiovascular mortality, but it remains unclear whether vitamin D deficiency is a cause or a consequence of a poor health status. Therefore, intervention studies are warranted to evaluate whether vitamin D supplementation reduces mortality and cardiovascular diseases.

25-hydroxyvitamin D levels, race, and the progression of kidney disease. Black individuals have lower 25-hydroxyvitamin D [25(OH)D] levels and experience a disproportionate burden of ESRD compared with white individuals. Animal studies suggest that vitamin D has renoprotective effects. We evaluated the contribution of low 25(OH)D levels on incidence of ESRD using data from the Third National Health and Nutrition Examination Survey-linked Medicare claims files (n = 13,328). We included baseline (1988 through 1994) measurements of 25(OH)D and assessed the incidence of ESRD through July 31, 2001. Overall, 34% of non-Hispanic black individuals had 25(OH)D levels <15 ng/ml compared with 5% of non-Hispanic white individuals (P < 0.001). During a median of 9.1 yr, 65 participants developed ESRD. After adjustment for demographic, socioeconomic, and clinical and laboratory factors (including diabetes, hypertension, estimated GFR, and albuminuria), participants with 25(OH)D levels <15 ng/ml had a 2.6-fold greater incidence of ESRD than those with levels > or =15 ng/ml (incidence rate ratio 2.64; 95% confidence interval [CI] 1.00 to 7.05; P = 0.05). After adjustment for clinical covariates but not 25(OH)D levels, non-Hispanic black individuals had a 2.83-fold (95% CI 1.03 to 7.77) higher risk for developing ESRD compared with non-Hispanic white individuals. Additional adjustment for 25(OH)D levels reduced the risk by 58% (incidence rate ratio 1.77; 95% CI 0.38 to 8.21). In summary, low 25(OH)D levels associate with development of ESRD even after adjustment for multiple risk factors. Low 25(OH)D levels may account for a substantial proportion of the increased risk for ESRD experienced by black individuals.

Understanding the different functions of vitamin D. Exposure of the skin to sunlight is now considered the most important source of vitamin D in Western countries. It is presumed to contribute approximately two thirds of the total requirement, leaving the remaining one third to the few foods naturally rich in this vitamin. In the skin, vitamin D is synthesized as a cholesterol chain which undergoes structural modifications following exposure to UVB rays. Once produced in the skin or absorbed in the gut as cholecalciferol, vitamin D enters the blood to be transported by a specific vitamin D binding protein, which is synthesized in the liver and has a powerful buffering capacity. The transport system carries the metabolites to the sites of further activation (25-hydroxylation in the liver and 1alpha-hydroxylation in the kidney), ultimately resulting in the production of calcitriol. This last compound, now regarded as a hormone, circulates freely in minimal amounts and, compared with the other metabolites, shows the highest affinity for the vitamin D receptor (VDR). The mechanism of VDR activation is rather complex, resulting in either stimulation or inhibition of protein synthesis. Importantly, besides its presence in parathyroid, bone, kidney and intestine, this receptor has been demonstrated in several tissues, where its stimulation results in a reduced proliferation rate and increased differentiation. Accordingly, vitamin D is now regarded as a complex hormonal system, involved not only in the regulation of divalent ions and bone, but also in the proliferation and differentiation of numerous cell types with potential involvement in several diseases like cancer, immune diseases, diabetes, hypertension and heart failure.
**Vitamin D status and arterial hypertension: a systematic review.** Vitamin D deficiency is common and is primarily caused by a lack of ultraviolet-B (UVB) radiation from reduced sun exposure, and the consequent limiting of vitamin D production in the skin. The vitamin D endocrine system regulates about 3% of the human genome. Observational data support the concept that vitamin D is involved in the pathogenesis of cardiovascular diseases and arterial hypertension. The antihypertensive properties of vitamin D include renoprotective effects, suppression of the renin-angiotensin-aldosterone system, direct effects on vascular cells, and effects on calcium metabolism, including prevention of secondary hyperparathyroidism. The results of clinical studies largely, but not consistently, favor the hypothesis that vitamin D sufficiency promotes lowering of arterial blood pressure. Randomized, placebo-controlled trials are greatly needed to clarify and definitively prove the effect of vitamin D on blood pressure. In general, the antihypertensive effects of vitamin D seem to be particularly prominent in vitamin-D-deficient patients with elevated blood pressure. Thus, in view of the relatively safe and inexpensive way in which vitamin D can be supplemented, we believe that vitamin D supplementation should be prescribed to patients with hypertension and 25-hydroxyvitamin D levels below target values.

**Treatment of vitamin D depletion after Roux-en-Y gastric bypass: a randomized prospective clinical trial.** BACKGROUND: A high prevalence (60%) of vitamin D (VitD) depletion, defined as a serum 25-hydroxyvitamin D level of < or =20 ng/mL, is present in preoperative morbidly obese patients. Despite daily supplementation with 800 IU VitD and 1500 mg calcium after Roux-en-Y gastric bypass (RYGB), VitD depletion persists in almost one half (44%) of patients. However, the optimal management of VitD depletion after RYGB and the potential benefits of such treatment are currently unknown. METHODS: A total of 60 VitD-depleted morbidly obese women were randomly assigned to receive 50,000 IU of VitD weekly after RYGB (group 1; n = 30) or no additional VitD after RYGB (group 2; n = 30). All patients received a daily supplement of 800 IU VitD and 1500 mg calcium. The serum calcium, parathyroid hormone, 25-hydroxyvitamin D, bone-specific alkaline phosphatase, urinary N-telopeptide, and bone mineral density were measured preoperatively and 1 year after RYGB. Questionnaires were used to assess other potential sources of VitD, including sunlight exposure and ingestion of VitD-containing foods/liquids. RESULTS: At 1 year after RYGB, VitD depletion and mean 25-hydroxyvitamin D level had improved significantly in group 1 (14% and 37.8 ng/mL, respectively) compared with the values in group 2 (85% and 15.2 ng/mL, respectively; P <.001 for both). A significant 33% retardation in hip bone mineral density decline (P = .043) and a significantly greater resolution of hypertension was seen in group 1 (75% versus 32%; P = .029). No significant adverse effects were encountered from pharmacologic VitD therapy. CONCLUSION: The results of our study have shown that 50,000 IU of VitD weekly after RYGB safely corrects VitD depletion in most women, attenuates cortical bone loss, and improves resolution of hypertension.

**Increased levels of 25 hydroxyvitamin D and 1,25-dihydroxyvitamin D after rosvastatin treatment: a novel pleiotropic effect of statins?** OBJECTIVES: Low levels of 25-hydroxyvitamin D are associated with higher risk of cardiovascular morbidity and mortality. Large trials demonstrated that statins significantly decrease cardiovascular morbidity and mortality. 7-dehydrocholesterol is the precursor of both cholesterol and vitamin D. The aim of this study was to investigate the possible effect of rosvastatin on vitamin D metabolism. METHODS: The study was performed in a prospective cohort design. The study group consisted of 91 hyperlipidemic patients who had not been treated with lipid lowering medications. Lipid parameters, 25 hydroxyvitamin-D, 1,25-dihydroxyvitamin D, and bone alkaline phosphatase were obtained at baseline and after 8 weeks of rosvastatin treatment. RESULTS: None of the subjects withdrew from the study because of the adverse effects. The mean age was 59.9 +/- 12.5 years. The majority of the patients were male (55, 60%). Seventeen patients were diabetic, and 43 patients had systemic hypertension. There was a significant increase in 25-hydroxyvitamin D, from mean 14.0 (range 3.7 - 67) to mean 36.3 (range 3.8 -117) ng/ml (p < 0.001), and also an increase of 1,25-dihydroxyvitamin D from mean 22.9 +/- 11.2 to 26.6 +/- 9.3 pg/dl (p = 0.023). Bone alkaline phosphatase decreased after 8 weeks of rosvastatin treatment, mean 17.7 (range 2.6-214) to mean 9.5 (range 2.3-19.1) u/l (p < 0.001) rosvastatin treatment. CONCLUSION: This study has shown an effect of rosvastatin on vitamin D metabolism, with an increase in both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D. This may be an
important pleiotropic effect whereby rosuvastatin reduces mortality in patients with coronary artery disease. Further studies are needed to clarify the relationship between statins and vitamin D metabolism.


**Vitamin D and cardiovascular disease.** Congestive heart failure is a chronic disease, whose incidence is especially growing in the subpopulation of elderly people. The majority of these patients have vitamin D levels in the insufficient range. Skin synthesis is the most important vitamin D source for humans. Congestive heart failure patients have relatively low outdoor activities. Consequently, a disease-related sedentary lifestyle is an important cause for the insufficient vitamin D status in patients. However, there is an accumulating body of evidence that vitamin D insufficiency plays a role in the etiology and pathogenesis of congestive heart failure. Vitamin D has direct effect on heart cells and indirect effect on the risk factors of the disease. Four major potential mechanisms may be important to explain the direct effects of vitamin D against congestive heart failure: the effect on myocardial contractile function, the regulation of natriuretic hormone secretion, the effect on extracellular matrix remodelling and the regulation of inflammation cytokines. **It has been demonstrated that vitamin D has a high impact on congestive heart failure main risk factors as hypertension, renin-angiotensin system malfunction and atherosclerosis. In spite of the robust preclinical data only few clinical observations prove the positive effect of vitamin D on congestive heart failure.**


**Baseline serum 25-hydroxy vitamin d is predictive of future glycemic status and insulin resistance: the Medical Research Council Ely Prospective Study 1990-2000.**

OBJECTIVE: Accumulating epidemiological evidence suggests that hypovitaminosis D may be associated with type 2 diabetes and related metabolic risks. However, prospective data using the biomarker serum 25-hydroxyvitamin D [25(OH)D] are limited and therefore examined in the present study. RESEARCH DESIGN AND METHODS: A total of 524 randomly selected nondiabetic men and women, aged 40-69 years at baseline, with measurements for serum 25(OH)D and IGF-1 in the population-based Ely Study, had glycemic status (oral glucose tolerance), lipids, insulin, anthropology, and blood pressure measured and metabolic syndrome risk (metabolic syndrome z score) derived at baseline and at 10 years of follow-up. RESULTS: Age-adjusted baseline mean serum 25(OH)D was greater in men (64.5 nmol/l [95% CI 61.2-67.9]) than women (57.2 nmol/l [54.4,60.0]) and varied with season (highest late summer). Baseline 25(OH)D was associated inversely with 10-year risk of hyperglycemia (fasting glucose: beta = -0.0023, P = 0.019; 2-h glucose: beta = -0.0097, P = 0.006), insulin resistance (fasting insulin beta = -0.1467, P = 0.010; homeostasis model assessment of insulin resistance [HOMA-IR]: beta = -0.0059, P = 0.005), and metabolic syndrome z score (beta = -0.0016, P = 0.048) after adjustment for age, sex, smoking, BMI, season, and baseline value of each metabolic outcome variable. Associations with 2-h glucose, insulin, and HOMA-IR remained significant after further adjustment for IGF-1, parathyroid hormone, calcium, physical activity, and social class.

CONCLUSIONS: This prospective study reports inverse associations between baseline serum 25(OH)D and future glycemia and insulin resistance. These associations are potentially important in understanding the etiology of abnormal glucose metabolism and warrant investigation in larger, specifically designed prospective studies and randomized controlled trials of supplementation.