Independent Association of Low Serum 25-Hydroxyvitamin D and 1,25-Dihydroxyvitamin D Levels With All-Cause and Cardiovascular Mortality

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Background: In cross-sectional studies, low serum levels of 25-hydroxyvitamin D are associated with higher prevalence of cardiovascular risk factors and disease. This study aimed to determine whether endogenous 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels are related to all-cause and cardiovascular mortality.

Methods: Prospective cohort study of 3258 consecutive male and female patients (mean [SD] age, 62 [10] years) scheduled for coronary angiography at a single tertiary center. We formed quartiles according to 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels within each month of blood drawings. The main outcome measures were all-cause and cardiovascular deaths.

Results: During a median follow-up period of 7.7 years, 737 patients (22.6%) died, including 463 deaths from cardiovascular causes. Multivariate-adjusted hazard ratios (HRs) for patients in the lower two 25-hydroxyvitamin D quartiles (median, 7.6 and 13.3 ng/mL [to convert 25-hydroxyvitamin D levels to nanomoles per liter, multiply by 2.496]) were higher for all-cause mortality (HR, 2.08; 95% confidence interval [CI], 1.60-2.70; and HR, 1.53; 95% CI, 1.17-2.01; respectively) and for cardiovascular mortality (HR, 2.22; 95% CI, 1.57-3.13; and HR, 1.82; 95% CI, 1.29-2.58; respectively) compared with patients in the highest 25-hydroxyvitamin D quartile (median, 28.4 ng/mL). Similar results were obtained for patients in the lowest 1,25-dihydroxyvitamin D quartile. These effects were independent of coronary artery disease, physical activity level, Charlson Comorbidity Index, variables of mineral metabolism, and New York Heart Association functional class. Low 25-hydroxyvitamin D levels were significantly correlated with variables of inflammation (C-reactive protein and interleukin 6 levels), oxidative burden (serum phospholipid and glutathione levels), and cell adhesion (vascular cell adhesion molecule 1 and intercellular adhesion molecule 1 levels).

Conclusions: Low 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels are independently associated with all-cause and cardiovascular mortality. A causal relationship has yet to be proved by intervention trials using vitamin D.

Arch Intern Med. 2008;168(12):1340-1349

Studies have demonstrated that low levels of vitamin D represent a problem of global dimension. A recent Workshop Consensus for Vitamin D Nutritional Guidelines estimated that about 50% and 60% of the older populations in North America and the rest of the world, respectively, do not have satisfactory vitamin D status. The consensus further concluded that the situation is similar in younger subjects. Reasons for this remain unclear but are likely related to factors such as urbanization, demographic shifts, decreased outdoor activity, air pollution and global dimming, and decreases in the cutaneous production of vitamin D with age. The amount of vitamin D from dietary sources is generally viewed as too insignificant in many regions of the world to have an effect on vitamin D status at the population level.

The minimum desirable serum level of 25-hydroxyvitamin D has been suggested to be 20 to 30 ng/mL (to convert 25-hydroxyvitamin D levels to nanomoles per liter, multiply by 2.496) according to the consensus conference and to a study in which the analysis was expanded to cover potential beneficial effects of vitamin D for multiple health outcomes. Low levels of 25-hydroxyvitamin D are clearly related to compromised bone mineral density, to falls and fractures, and to diminished lower extremity function. In addition to higher incidences of cancer and immune dysfunction, low levels of 25-hydroxyvitamin D have been re-

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ently linked to the presence of cardiovascular disease, hypertension, and the metabolic syndrome. Results of recent nationwide investigations showed an association of low 25-hydroxyvitamin D levels with important cardiovascular risk factors and further supported the findings of preclinical and clinical investigations that demonstrated positive effects of vitamin D and its analogues on fibrinolysis, blood lipids, thrombogenicity, endothelial regeneration, and smooth muscle cell growth. Together, these findings strongly suggest that 25-hydroxyvitamin D has beneficial effects, some involving the cardiovascular system, that are independent of calcium metabolism.

The mediator of these effects is thought to be 1,25-dihydroxyvitamin D, produced by the kidney, by extra renal tissues (such as the vasculature), and by immune and gastrointestinal cells that express 1α-hydroxylase, which converts 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. Locally produced 1,25-dihydroxyvitamin D may act in an autocrine or a paracrine manner via activation of the vitamin D receptor, which is found in many different cell types throughout the body. Because the serum level of 25-hydroxyvitamin D is roughly 1000-fold higher and the affinity for vitamin D receptor 100-fold lower compared with 1,25-dihydroxyvitamin D, direct effects of 25-hydroxyvitamin D on gene transcription or activation by the vitamin D receptor 100-fold lower compared with its analogues on fibrinolysis, blood lipids, thrombogenicity, endothelial regeneration, and smooth muscle cell growth. Together, these findings strongly suggest that 25-hydroxyvitamin D has beneficial effects, some involving the cardiovascular system, that are independent of calcium metabolism.

The Ludwigshafen Risk and Cardiovascular Health (LURIC) study is a prospective cohort trial designed to evaluate the effect of genetic polymorphisms and plasma biomarkers on cardiovascular health. Patients were recruited between July 1, 1997, and January 14, 2000, at the Herzzentrum Ludwigshafen (Cardiac Center Ludwigshafen) in southwest Germany (49° 29 minutes north latitude). The rationale and design of this study, baseline characteristics of the population, and definitions used for diagnosis of diabetes mellitus and hypertension have been published previously. In brief, our study population comprised 3316 patients of white race/ethnicity referred for coronary angiography in a tertiary care medical center. Serum levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D were determined in 3288 patients (98.3% of the entire study population; mean [SD] age, 62 [10] years), and the analysis was restricted to this group. Study participants had to demonstrate a stable clinical condition except for acute coronary syndrome. Exclusion criteria were any acute illness other than acute coronary syndrome, any predominant noncardiac chronic disease, and a history of malignant neoplasm(s) within the past 5 years. Seventy-eight patients (2.4%) reported taking vitamin supplements on a regular basis, which usually contained B complex vitamins or vitamin D. Because 25-hydroxyvitamin D levels (mean [SD], 22.1 [11.3] ng/mL) were only slightly higher in users of vitamin D preparations compared with the remaining cohort (mean [SD], 17.2 [9.1] ng/mL) and because age, PTH levels, and 1,25-dihydroxyvitamin D levels did not differ significantly, we decided to include these patients in the present analysis. Written informed consent was obtained from each participant, and the study was approved by the institutional review board at the Ärztekammer Rheinland-Pfalz (Medical Association of Rheinland-Pfalz).

Coronary angiography was commonly indicated because of clinical symptoms or results of noninvasive tests that suggested myocardial ischemia. Coronary artery disease (CAD) was defined as the presence of at least 50% stenosis of at least 1 of 15 segments of the 3 major coronary arteries, based on maximal luminal narrowing. We used the Charlson Comorbidity Index, which has been shown to be a valid and reliable instrument to assess comorbidity, to form 3 groups of patients with 0 score points (group 0), 1 score point (group 1), and 2 or more score points (group 2). A questionnaire with a scoring system ranging from 1 to 11 was used to classify the mean physical activity levels, and study participants were grouped into the following 3 categories of physical activity: below average (score, 1-3), average (score, 4-7), and above average (score, ≥8).

LABORATORY ANALYSIS

A fasting venous blood sample was obtained in the morning before coronary angiography. Selected variables were measured after samples were snap frozen and stored at –80°C. A summary of methods and test kits used for variables relevant to this study has been published. The estimated glomerular filtration rate was calculated according to the 4-variable model of the Modification of Diet in Renal Disease study. Serum levels of 25-hydroxyvitamin D were assayed on a weekly basis using a radioimmunoassay (DiaSorin SA, Antony, France) with intra-assay and interassay coefficients of variation of 8.6% and 9.2%, respectively. In a random sample of 100 study participants, 25-hydroxyvitamin D level was also determined using liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) with isotopically labeled internal standard and 2 fragment mass to charge ratios of 401.4 to 382.2 (quantifier) and 401.4 to 365.3 (qualifier). Another fragment (mass to charge ratio, 413.5 to 395.4) was used to monitor 25-hydroxyvitamin D level, but none could be detected in any of the samples. A highly significant correlation was noted between 25-hydroxyvitamin D levels obtained by radioimmunoassay and by LC-MS/MS (r = 0.875, P < .001). Levels of 1,25-dihydroxyvitamin D (Ni- chols Institute Diagnostika GmbH, Bad Nauheim, Germany) were measured by radioimmunoassay on a multicrystal counter (Berthold LB2014, DiaSorin SA). Intra-assay and

METHODS

STUDY POPULATION

The Ludwigshafen Risk and Cardiovascular Health (LURIC) study is a prospective cohort trial designed to evaluate the effect of genetic polymorphisms and plasma biomarkers on cardiovascular health. Patients were recruited between July 1, 1997, and January 14, 2000, at the Herzzentrum Ludwigshafen (Cardiac Center Ludwigshafen) in southwest Germany (49° 29 minutes north latitude). The rationale and design of this study, baseline characteristics of the population, and definitions used for diagnosis of diabetes mellitus
interassay coefficients of variation were below 10% for all described laboratory procedures.

**FOLLOW-UP**

Information on mortality was obtained from local registries. We used death certificates to classify the deceased into those who died from cardiovascular vs noncardiovascular causes. This classification was done independently by 2 experienced clinicians who were blinded to any data on the study participants except the already-mentioned information that was required to classify the causes of death. In the event of disagreement or uncertainty concerning the cause of death, the decision was made by one of us who is a principal investigator of the LURIC study (W.M.). Eighteen patients could not be contacted for follow-up, and for 23 of the deceased we had insufficient information to classify the cause of death. The latter study participants were included in the analysis of all-cause mortality but were excluded from any statistical procedure regarding cardiovascular mortality.

**STATISTICAL ANALYSIS**

Because serum vitamin D levels fluctuate by month throughout the year, we decided for the purpose of this analysis not to use absolute vitamin D levels but instead to categorize individual patients’ 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels into quartiles that were obtained on the basis of 202 to 358 vitamin D measurements of study patients each month. To address other possibilities of 25-hydroxyvitamin D categorization and to allow for comparisons with the quartile-based approach already mentioned, these results are also briefly mentioned in the “Comment” section.

Baseline characteristics of the 25-hydroxyvitamin D groups are given as percentages for categorical data and as medians with interquartile ranges for continuous variables. Comparisons between groups were performed using the χ² test for categorical data and using analysis of variance and analysis of covariance with P for trend and adjustments as indicated for continuous data. If appropriate, continuous variables were logarithmically transformed before use in parametric procedures. Kaplan-Meier curves followed by log-rank test were used to evaluate differences in overall and cardiovascular mortality for 25-hydroxyvitamin D categories. Hazard ratios with 95% confidence intervals (CIs) for all-cause and cardiovascular mortality were calculated using Cox proportional hazards regression models. Hazard ratios for 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D categories were calculated by comparing the data with those of the highest 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D quartiles, respectively. We adjusted for several possible confounders in the Cox proportional hazards regression model by using different models that included important clinical variables, cardiovascular risk factors, or factors related to calcium metabolism. The backward stepwise logistic regression selection method was used, and the results of the final step are given. We tested for plausible interactions between the covariates by adding product terms to our models, and we tested for linearity. Further assumptions underlying the Cox proportional hazards regression model were evaluated by log minus log survival and partial (Schoenfeld) residuals vs survival time plots and were found valid. All statistical tests were 2-sided, and statistical significance was defined as P < .05. All data were analyzed using commercially available statistical software (SPSS 15.0; SPSS Inc, Chicago, Illinois).

**RESULTS**

**MORTALITY RATES**

After a median follow-up of 7.7 years, 737 persons (22.6% of the study population at baseline) had died. Of these, 463 deaths (62.8%) were from cardiovascular causes, 251 (34.1%) were from noncardiovascular causes, and 23 (3.1%) could not be classified because of insufficient data about the cause of death. Among patients with angiographic CAD, 319 deaths occurred from cardiovascular causes and 148 deaths from noncardiovascular causes.

**25-HYDROXYVITAMIN D LEVELS**

Significant seasonal changes in serum 25-hydroxyvitamin D levels were found, with the lowest and highest levels appearing in March (mean [SD], 12.0 [6.8] ng/mL) and in August (mean [SD], 22.7 [9.6] ng/mL) (P < .001, analysis of variance), corresponding to an 89% difference in the mean levels. When patients were grouped into different 25-hydroxyvitamin D categories (0-10, >10-20, >20-25, >25-30, and >30 ng/mL), PTH levels began to rise significantly with the category of greater than 20 to 25 ng/mL. Respective increases in PTH levels averaged 3 pg/mL (to convert PTH levels to nanograms per liter, multiply by 1.0) (for the >20-25 ng/mL category), 5 pg/mL (for the >10-20 ng/mL category), and 12 pg/mL (for the 0-10 ng/mL category). Because 25-hydroxyvitamin D levels vary with the month of the year, the range of 25-hydroxyvitamin D quartiles fluctuates as well (Figure 1).

**BASELINE CHARACTERISTICS**

Baseline characteristics according to 25-hydroxyvitamin D quartiles are summarized in Table 1. On average, patients in the lowest 25-hydroxyvitamin D quartile were older, were more likely to be female, and had more comorbidities. The mean serum PTH levels were...
Table 1. Baseline Characteristics According to 25-Hydroxyvitamin D Quartiles

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1st (n = 836)</th>
<th>2nd (n = 802)</th>
<th>3rd (n = 813)</th>
<th>4th (n = 807)</th>
<th>P Value a</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-Hydroxyvitamin D level, ng/mL, median (IQR)</td>
<td>7.6 (5.8-10.1)</td>
<td>13.3 (10.4-16.8)</td>
<td>18.9 (14.6-22.8)</td>
<td>28.4 (23.6-33.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>66.3 (58.4-73.4)</td>
<td>64.3 (56.3-70.8)</td>
<td>62.7 (55.6-69.5)</td>
<td>61.5 (55.0-67.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>44.1</td>
<td>28.6</td>
<td>25.0</td>
<td>23.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Body mass index, median (IQR)</td>
<td>27.4 (24.5-30.4)</td>
<td>27.3 (24.8-30.1)</td>
<td>27.2 (25.0-29.7)</td>
<td>26.7 (24.6-29.0)</td>
<td>.006</td>
</tr>
<tr>
<td>Waist to hip ratio, median (IQR)</td>
<td>0.96 (0.91-1.01)</td>
<td>0.97 (0.92-1.02)</td>
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<td>0.96 (0.91-1.00)</td>
<td>.61</td>
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<tr>
<td>Charlson Comorbidity Index category, %</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Group 0</td>
<td>17.8</td>
<td>28.4</td>
<td>28.3</td>
<td>31.6</td>
<td>&lt;.001</td>
</tr>
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<td>Group 1</td>
<td>27.8</td>
<td>29.6</td>
<td>36.7</td>
<td>37.7</td>
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</tr>
<tr>
<td>Group 2</td>
<td>54.4</td>
<td>42.1</td>
<td>35.0</td>
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<td>Physical activity level, %</td>
<td>36.9</td>
<td>26.7</td>
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<td>New York Heart Association functional class, %</td>
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</tr>
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<td>Average</td>
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<td></td>
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<tr>
<td>Above average</td>
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<td>18.0</td>
<td>21.6</td>
<td>29.2</td>
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<td>Serum cholesterol, median (IQR), mg/dL</td>
<td>13.4 (12.3-14.5)</td>
<td>13.9 (13.1-15.0)</td>
<td>14.0 (13.1-15.0)</td>
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<td>Serum triglyceride, median (IQR), mg/dL</td>
<td>79 (66-92)</td>
<td>81 (70-92)</td>
<td>81 (71-93)</td>
<td>82 (71-92)</td>
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<td>Serum Cystatin C, median (IQR), mg/L</td>
<td>0.96 (0.83-1.15)</td>
<td>0.93 (0.81-1.08)</td>
<td>0.89 (0.79-1.02)</td>
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<td>Glomerular filtration rate, median (IQR), mL/min-1.73 m²</td>
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Abbreviations: BNP, brain natriuretic peptide; IQR, interquartile range.

St conversion factors: To convert 25-hydroxyvitamin D levels to nanomoles per liter, multiply by 2.496; 1,25-dihydroxyvitamin D levels to picomoles per liter, multiply by 2.6; hemoglobin levels to grams per liter, multiply by 10.0; cholesterol levels to millimoles per liter, multiply by 0.0259; triglyceride levels to millimoles per liter, multiply by 0.0113; calcium levels to millimoles per liter, multiply by 0.25; magnesium levels to millimoles per liter, multiply by 0.50; parathyroid hormone levels to nanograms per liter, multiply by 1.0.

a Analysis of variance for categorical variables and χ² test for categorical variables.

b Calculated as weight in kilograms divided by height in meters squared.

36% higher and the 1,25-dihydroxyvitamin D levels 31% lower among patients in the lowest 25-hydroxyvitamin D quartile compared with those in the highest quartile. Differences in corrected serum calcium and phosphate levels were absent or small.

**SURVIVAL STATISTICS**

Kaplan-Meier curve analysis followed by log-rank test showed that risk for all-cause and cardiovascular mortality increases significantly (P < .001) across 25-hydroxyvitamin D quartiles (Figure 2). Hazard ratios (with 95% CIs) for all-cause mortality (Table 2) and for cardiovascular mortality (Figure 3) among 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D quartiles are given for 3 different statistical models that include traditional cardiovascular risk factors or other variables directly or indirectly correlated with vitamin D metabolism. After adjustment for the respective other serum vitamin D level, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D associations with all-cause and cardiovascular mortality remained significant.
We performed a multivariate-adjusted subgroup analysis (based on covariates of model 3, described in the legend to Figure 3) for all-cause mortality among patients in different Charlson Comorbidity Index, New York Heart Association functional class, and physical activity level categories. These results are shown in Figure 4.

**CORRELATION OF 25-HYDROXYVITAMIN D LEVELS WITH 1,25-DIHYDROXYVITAMIN D LEVELS**

Univariate correlation analysis between 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels was weak \( r = 0.36, P < .001 \) even after adjustment for cystatin C levels \( r = 0.32, P < .001 \). Patients in a given 25-hydroxyvitamin D category could have 1,25-dihydroxyvitamin D serum levels ranging from low to high (Figure 5A). Patients’ concurrent assignment to both vitamin D quartiles suggests a synergistic increase in all-cause mortality within a respective 25-hydroxyvitamin D or 1,25-dihydroxyvitamin D quartile with declining levels of the respective other vitamin D level (Figure 5B).

**MORTALITY RISK IN PATIENTS WITHOUT SIGNIFICANT CAD**

We split the results of multivariate-adjusted Cox proportional hazards regression models by different categories of angiographic CAD. A total of 2190 patients (67.3%) had significant CAD \( (\geq 50\%) \) stenosis. Six hundred ninety-three patients had virtually no CAD \( (<20\%) \) stenosis. Even in patients with CAD of less than 50% stenosis or less than 20% stenosis, there was a gradual increase in all-cause mortality for all lower 25-hydroxyvitamin D or 1,25-dihydroxyvitamin D quartiles (Figure 6).

**CARDIOVASCULAR RISK MARKERS**

We performed multivariate-adjusted comparisons among 25-hydroxyvitamin D quartiles for biological markers potentially linked to cardiovascular risk (Table 3). In addition, multiple linear regression analyses were performed for 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels, which were found to be correlated with the following log values (significant for all 25-hydroxyvitamin D correlations and for most 1,25-dihydroxyvitamin D correlations): glutathione, interleukin 6, phospholipids, C-reactive protein, intercellular adhesion molecule 1, and vascular cell adhesion molecule 1, with standard \( \beta \) coefficients of 0.10 to 0.20 \( (P < .001\) for all) after adjustments for age, sex, body mass index, and physical activity and level of 0.05 to 0.10 after additional multivariate adjustments. The direction of these correlations pointed toward an increase in cardiovascular risk at low vitamin D levels. Variables available for all patients (C-reactive protein and phospholipid levels) were also added to multivariate Cox proportional hazards regression models and were found not to significantly affect the vitamin D mortality relationship.
creases in serum PTH levels, decreases in physical performance, and diminished lower extremity function. Using such a vitamin D classification, we calculated multiplicative hazard ratios for patients with vitamin D deficiency (adjusted HR, 3.04; 95% CI, 1.95-4.75). Therefore, it can be concluded that patients having 25-hydroxyvitamin D values above the 10th percentile (adjusted HR, 4.91; 95% CI, 3.33-7.20; and adjusted HR, 3.04; 95% CI, 1.95-4.75). Therefore, it cannot be excluded that risk gradients become even steeper when outcomes are compared with 25-hydroxyvitamin D levels well above those seen in our study population.

At first glance, the percentage of patients with low 25-hydroxyvitamin D values seems unexpectedly high in the present study. Roughly two-thirds had serum levels below 20 ng/mL. However, our mean value of 17.3 ng/mL compares well with values reported from other large trials performed in middle European countries such as France, Italy, and Germany. Another important aspect supporting our conclusions is that, similar to low 25-hydroxyvitamin D levels, low 1,25-dihydroxyvitamin D levels were associated with increased HRs for mortality, despite a weak correlation between the two (r = 0.36). This leads to the conclusion that 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels may yield similar but independent biologic effects. This is also in line with our finding that, when both variables are considered concomitantly, a synergistic effect on mortality risk seems evident (Figure 5B).
and renal function (partial $R^2=7.3\%$ for log cystatin C) constituted the 2 most important independent predictors in the model, yielding an overall $R^2$ of 24%. We were unable to find an independent association with age, despite a study demonstrating such an effect on 1,25-dihydroxyvitamin D production after infusion of PTH fragment 1-34. Consequently, availability of 25-hydroxyvitamin D substrate and renal function account for a small explainable proportion of 1,25-dihydroxyvitamin D serum levels. The question remains whether extrarenal production of 1,25-dihydroxyvitamin D contributes, at least in part, to the circulating pool of 1,25-dihydroxyvitamin D in individuals with normal renal function.

Another interesting aspect of the present study is that the association of vitamin D levels with mortality can be compared between patients with and without CAD. Low 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels were associated with significant increases in all-cause mortality but were consistently higher in patients without significant CAD. We conclude from these data that low 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels seem to be important mediators of mortality even when there is little or no indication of overt vascular disease.

A limitation of our study is that we are unable to decide whether the association between low 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels and mortality is causal or not. However, there are a few indications pointing to a possible link. Elevated C-reactive protein and interleukin 6 levels in patients with lower 25-hydroxyvitamin D levels suggests that 25-hydroxyvitamin D has anti-inflammatory properties. Similar relationships have been reported by others.
increased susceptibility to arterial calcification,35,36 or an increase in renin messenger RNA expression.37

...of column L (both low) the highest mortality rates during the study period.

...the overall correlation between the 2 endogenous D vitamins was weak (r = 0.32, P < .001). B, Effects on mortality rates when 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels were considered concomitantly high (column H) or concomitantly low (column L) levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D were frequent, the overall correlation between the 2 endogenous D vitamins was weak (r = 0.32, P < .001). B, Effects on mortality rates when 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D quartiles. Although serum vitamin D levels among patients assigned to different categories may be associated with mortality in-...
Study concept and design: Harald Dobnig, MD, Division of Endocrinology and Nuclear Medicine, Department of Internal Medicine (Dr Dobnig), and Clinical Institute of Medical and Chemical Laboratory Diagnostics (Drs Scharnagl, Renner, and Maerz and Ms Weihrauch), Medical University of Graz, Graz, Austria; and Department of Public Health, Social and Preventive Medicine, Mannheim Medical Faculty, University of Heidelberg, Heidelberg (Dr Pilz), LURIC Study Nonprofit LLC, Freiburg (Ms Seelhorst and Dr Wellnitz), Synlab Center of Laboratory Diagnostics Stuttgart, Leinfeld-Echterdingen (Dr Kinkeldei), Division of Endocrinology and Diabetes, Department of Internal Medicine, University of Ulm, Ulm (Dr Boehm), and Synlab Center of Laboratory Diagnostics Heidelberg, Eppelheim (Dr Maerz), Germany.

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Financial Disclosure: None reported.

Funding/Support: The LURIC study has received unrestricted grants from Sanofi-Aventis, Roche, Dade Behring, and AstraZeneca.

Additional Contributions: The German registration offices and local public health departments assisted with the study. Eugenia Lamont and Günter J. Krejs, MD, critically reviewed the manuscript, and Andrea Groselj-Strele, MSc, provided statistical advice. We thank the participants of the LURIC study, the LURIC study team, and the laboratory staff at the Ludwigshafen General Hospital, the University of Freiburg, and the University of Ulm.

Table 3. Associations of 25-Hydroxyvitamin D Quartiles With Cardiovascular Risk Markersa

<table>
<thead>
<tr>
<th>Variable</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>P Value for Trendb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Markers of inflammation, mean (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein level, mg/dL</td>
<td>3.94 (3.61-4.30)</td>
<td>3.52 (3.24-3.84)</td>
<td>3.08 (2.83-3.35)</td>
<td>3.39 (3.11-3.70)</td>
<td>.005</td>
</tr>
<tr>
<td>Interleukin 6 level, mg/L</td>
<td>5.27 (4.56-6.01)</td>
<td>4.15 (3.65-4.72)</td>
<td>4.07 (3.63-4.57)</td>
<td>3.55 (3.16-3.99)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Markers of cell adhesion, mean (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercellular adhesion molecule 1 level, mg/L</td>
<td>254 (248-259)</td>
<td>245 (240-259)</td>
<td>242 (236-247)</td>
<td>241 (235-247)</td>
<td>.003</td>
</tr>
<tr>
<td>Vascular cell adhesion molecule 1 level, mg/L</td>
<td>776 (759-793)</td>
<td>762 (744-780)</td>
<td>757 (738-774)</td>
<td>748 (729-769)</td>
<td>.05</td>
</tr>
<tr>
<td>Markers of oxidative stress, mean (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glutathione level, µmol/L</td>
<td>3.54 (3.42-3.67)</td>
<td>3.89 (3.76-4.04)</td>
<td>4.19 (4.05-4.33)</td>
<td>4.08 (3.94-4.23)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Phospholipid level, mg/dL</td>
<td>212 (209-214)</td>
<td>216 (214-218)</td>
<td>216 (214-219)</td>
<td>218 (216-220)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

SI conversion factor: To convert C-reactive protein levels to nanomoles per liter, multiply by 9.524.

a Analysis of covariance with adjustments for age, sex, active smokers, acute infection, diabetes mellitus, systemic hypertension, body mass index, cystatin C level, physical exercise level, N-terminal pro-BNP level, and low-density lipoprotein cholesterol level.

REFERENCES


