A reverse J-shaped association of all-cause mortality with serum 25-hydroxyvitamin D in General Practice, the CopD-Study*

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Introduction

Background

Optimal levels of vitamin D have been a topic of heavy debate and the correlation between 25-hydroxyvitamin D levels and mortality still remains to be established.

Aims

To determine the association between all-cause mortality and serum levels of 25-hydroxyvitamin D, calcium, and parathyroid hormone.

Data Collection

A database from the General Practitioners Laboratory of Copenhagen (GPLC) containing values from blood samples collected from the Copenhagen area (population 1.1 million), was accessed in this retrospective, observational cohort study. 247,574 unique blood samples collected during the period 2004.04.29 to 2010.01.22 were included. The study protocol was approved by the Danish Data Protection Agency.

Results

During follow-up (median 3.07 yr), 15,198 (6%) of the 247,574 subjects died. A reverse J-shaped association between serum level of 25-hydroxyvitamin D (25(OH)D) and mortality was observed (Fig. 1A). A serum 25(OH)D level of 50-60 nmol/l was associated with the lowest mortality risk. Compared to 50 nmol/l, the hazard ratios (95% CI) of all-cause mortality at very low (10 nmol/l) and high (140 nmol/l) serum levels of 25(OH)D were 2.13 (2.02-2.24) and 1.42 (1.31-1.53), respectively.

Similarly, both high and low levels of albumin adjusted serum calcium and PTH were associated with an increased mortality (Fig. 2B-C), also secondary hyperparathyroidism was associated with higher mortality (p < 0.0001) (data not shown).

Vitamin D insufficiency was prevalent in the study population (Table 1) and 10.5% suffered from secondary hyperparathyroidism (Table 2).

Table 1: Prevalence of vitamin D deficiency in the study

<table>
<thead>
<tr>
<th>Vitamin D level (nmol/l)</th>
<th>All</th>
<th>Women</th>
<th>Man</th>
<th>p-value (gender difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VITD&lt;12.5</td>
<td>54.4%</td>
<td>55.5%</td>
<td>53.4%</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>VITD&lt;25</td>
<td>20.5%</td>
<td>21.3%</td>
<td>19.8%</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>VITD&gt;12.5</td>
<td>4.8%</td>
<td>4.7%</td>
<td>5.0%</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

Methods

Serum 25(OH)D assays: 25(OH)D was determined in samples at GPLC with the commercially available assays, the LIAISON 25 OH Vitamin D assay, D4Serum and D77E4 25-hydroxyvitamin D, Immunodiagnostics systems (SD) Ltd. The assays determine the sum of 25-hydroxy-vitamin D3 and 25-hydroxy-vitamin D2.

S/PTH Assay: S/PTH was determined in samples with the commercially available ADVIA 1800 PTH kit Siemens. Calcium and total calcium were determined in serum by the LIAISON Calcium assay (Dade-Behring, USA). Each serum sample was tested in duplicate.

Results were considered in samples by the ADVIA Chemistry System (Bayer/Siemens) Creatinine (Creat) kit according to the instructions of the manufacturer. The inter-assay CV was 2.1% (at 36.1 mg/l) and 1.7% (at 210 mg/l).

Albumin adjusted calcium was calculated as: Total Calcium (mmol/l) = 0.1895 (41.3 - Albumin in g/l) + 1.13

Creatinine was determined in serum by the commercially available ADVIA Chemistry System (Bayer/Siemens) Creatinine (Creat) kit according to the instructions of the manufacturer. The inter-assay CV was 2.3% (at level 92 µmol/l and level 527 µmol/l).

Statistical Analysis: Statistical Analyses were performed using SAS statistical software (SAS Institute Inc., Cary, NC).

Figure 1: Distribution of place of blood sampling. More than 90% of the blood samples were taken in the general practice or at the General Practitioners Laboratory of Copenhagen. All blood samples were analyzed by this central laboratory.

Figure 2: Hazard ratios of all-cause mortality by restricted cubic spline Cox regression analysis. Estimates were adjusted for age, sex and season of blood sampling according to (A) serum 25-hydroxyvitamin D level with 50 nmol/l as the reference value (B) Albumin adjusted serum calcium level with 2.35 mmol/l as the reference value (C) serum PTH level with 4.5 pmol/l as the reference value.

In this study from general practice a reverse J-shaped relation between serum level of 25-hydroxyvitamin D and all-cause mortality was observed, indicating not only a lower limit but also an upper limit of serum 25-hydroxyvitamin D levels. The lowest mortality risk was at 50-60 nmol/l.

Similarly, both high and low levels of albumin adjusted serum calcium and PTH were associated with an increased mortality and also secondary hyperparathyroidism was associated with higher mortality (p<0.0001).

The study did not allow inference of causality and further studies are needed to elucidate a possible causal relationship between 25(OH)D level (especially higher levels) and mortality.

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