Vitamin D Status and Mortality: Meta-Analysis of Individual Participant Data Confirms Strong Association

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Abstract: Scientists and physicians have suggested that poor vitamin D intake can result in increased cardio-vascular mortality. Also total mortality appears to be increased with poor vitamin D status. A research team of the German Cancer Research Center in Heidelberg (DKFZ) headed by Ben Schöttker was able to demonstrate this association in a meta-analysis of 8 European and US-based cohort studies. In addition, serum 25(OH)D concentration (calcidiol) was shown to constitute a prognostic parameter in patients with a history of cancer.

Key words: vitamin D, vitamin D status, calcidiol, meta-analysis

Introduction

Vitamin D is the pre-hormone of calcitriol, a pleiotropic active steroid hormone. It is well known for its action on bone-metabolism; but also the immune system and the cardio-vascular system, as well as cell proliferation are influenced by calcitriol [1–8]. Observational studies have repeatedly demonstrated a relation between the occurrence of cardio-vascular diseases and vitamin D status. Furthermore, poor vitamin D supply showed to be a risk factor with respect to cardio-vascular and cancer-related mortality. In a recently published meta-analysis of 73 cohort studies with approximately 850,000 subjects published in the British Medical Journal, comparing bottom vs. top thirds of baseline circulating calcidiol, pooled relative risks were 1.14 (95% CI 1.01–1.29) for death from cancer [9]. Earlier meta-analyses have shown similar results [10–11].

However, until today, it was not possible to clearly demonstrate a dose-response relation, as earlier meta-analyses were based on published study results and not on participant data. It also cannot be excluded that a low vitamin D serum level does not represent the cause of the increased mortality, but rather constitutes a marker of unhealthy life style or certain diseases.

The research team around Schöttker [12] therefore analysed the original data of 8 cohort studies from 16 European countries and the US. Their assessment included data from 26,018 study participants aged
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between 50 and 79 years. The median follow-up period of the individual studies ranged from 4.2 to 15.8 years. In their statistical analysis, risk factors including age, gender, education level, BMI, smoking habits, and physical activity were considered. In a separate analysis, the anamneses of known diseases, which may have confounded the results, were further considered.

The results, published in the British Medical Journal, revealed the following [12]:

- **Vitamin D status by baseline characteristics of the study population.** Median calcidiol serum concentration of the individual cohorts ranged between 24 and 62 nmol/L. Similar to earlier studies, smokers and overweight subjects had generally lower serum levels. In contrast, persons with a higher educational level and physically active people were generally well supplied with vitamin D. Age did not show a relation to vitamin D status. Also subjects with or without respective medical history (e.g. diabetes, cardiovascular disease, cancer) did not differ in their vitamin D status.

- **Vitamin D status and mortality.** During the course of the study, 6695 subjects died, 2624 cases due to cardiovascular mortality, 2227 died of cancer. Subjects in the lowest quintile of calcidiol concentration showed a 1.6-fold increase in total mortality risk compared to well supplied persons (highest quintile, RR 1.57; 95 % CI: 1.36 – 1.81). A similar relation was revealed for the endpoints cardiovascular mortality and cancer mortality. Exempted were subjects without previous cancer history, i.e. no relation was found between vitamin D status and mortality (table I).

- **Dose-response relation.** A curvilinear inverse association for all-cause mortality across all calcidiol quintiles was found. A clearly diminished risk was shown for calcidiol concentrations above the 50th percentile of the population, i.e. the half of the population with highest calcidiol concentrations (figure 1). A similar association was disclosed for the endpoint “cardiovascular mortality” (with or without previous history). Also cancer mortality risk decreased continuously. However, this was

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Relative risk (95% CI)</th>
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<tbody>
<tr>
<td>Total mortality</td>
<td>1.57 (1.18-1.68)</td>
</tr>
<tr>
<td>Cancer mortality in subjects without history of cancer</td>
<td>1.03 (0.89-1.29)</td>
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<tr>
<td>Cancer mortality in subjects with history of cancer</td>
<td>1.70 (1.00-2.88)</td>
</tr>
<tr>
<td>Cardio-vascular mortality in subjects without history of cardiovascular disease</td>
<td>1.41 (1.18-1.68)</td>
</tr>
<tr>
<td>Cardiovascular mortality with history of cardiovascular disease</td>
<td>1.65 (1.22-2.22)</td>
</tr>
</tbody>
</table>

1Compared were the lowest against the highest quintile of serum calcidiol-concentration. Data was adjusted for established risk-factors including age, gender, education-level, BMI, smoking habits and physical activity.

**Figure 1:** Dose-response relation between serum calcidiol concentration and total mortality [12]

**Figure 2:** Dose-response relation between serum calcidiol concentration and cancer mortality in subjects without previous cancer history (a) and in subjects with previous cancer history (b) [12].

Table I: Calcidiol and mortality [12].
true only for subjects with previous cancer history; without previous history, there were no signs of a dose-response relation (figure 2).

Conclusions

The results of this meta-analysis, based for the first time on individual participant data, support the recommendation that elderly people should respect a sufficient vitamin D intake. In an earlier work, Schöttker et al. recommended serum levels above 50 nmol/L (or 20 ng/mL) calcidiol [13]. This threshold should be reached to prevent fractures following falls, and premature death in the elderly (≥65 years, for both men and women). This desired target level can be reached in 90–95% of the population with an intake of 20 μg vitamin D/day, 25 μg/day will ensure this for 95–97.5%. Nutrition societies such as the German Nutrition Society (DGE), the International Osteoporosis Foundation (IOF) or the US Institute of Medicine (IOM) have therefore recommended a vitamin D intake of 20 μg per day for adults when endogenous synthesis is missing [14]. Whether vitamin D supplementation will indeed be able to lower the mortality of the elderly is currently examined in the British Vidal (vitamin D and longevity) study; first results are expected in 2017.

References
