Vitamin D, precocious acute myocardial infarction, and exceptional longevity

Running title: 25(OH)D in centenarians

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Recent studies have reported low circulating levels of 25-hydroxyvitamin D (25(OH)D), the biologically active form of vitamin D, in patients with cardiovascular disease (CVD) [1], hypertension [2], carotid atherosclerosis [3], atrial fibrillation [4], and heart failure [5]. Moreover, vitamin D deficiency has been associated with all-cause mortality [6,7] and predicts adverse cardiac events in patients with established CVD [8] or after acute myocardial infarction (AMI) [9]. In turn, vitamin D supplementation improves the modulation of autonomic tone [10].

Although centenarians (ie, ≥100 years; 20+ years more than the average life expectancy in the Western world) represent the paradigm for exceptional longevity (EL), they are usually an heterogenous group of subjects who can either delay (‘delayers’), survive (‘survivors’) and even escape (‘dodgers’) common age-related diseases [11]. In contrast, precocious AMI is commonly considered a good pathophysiological model of poor human healthy status, being associated with early mortality [12-14]. Higher concentrations of 25(OH)D predict subsequent lower 13-year total mortality and incident CVD [15]. Low levels of 25(OH)D have also been associated with poor physical function (notably with poor grip strength) in people aged 98+ years [16]. This is an important consideration because preservation of muscle strength late in life is a key issue in the functional capacity and health status of long-lived individuals [16].

In the current study, we sought to investigate whether serum 25(OH)D levels can be associated with healthy EL. To achieve this goal, three groups of subjects were enrolled: i) centenarians free of age-related illnesses, ie, ‘dodgers’ (n=79, 100–104 years, 49% males), ii) patients with precocious AMI (ie, occurring before 40 years of age; n=178, 27–39 years, 57% males), iii) and apparently healthy adults who were matched for age and sex to AMI patients (n=180, 28–39 years, 57% males). All subjects
were Caucasian whites ascertained to be of Italian descent. The main clinical characteristics of the study participants have been previously reported [12,13]. Briefly, all of the centenarians were free of hypertension, obesity, hypercholesterolemia, and hypertriglyceridemia. All patients with precocious AMI were free of diabetes but some had hypertension (36%), obesity (21%), hypercholesterolemia (54%), or hypertriglyceridemia (22%) [12,13]. The study complied with the tenets of the Declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained from all participants.

Blood samples were obtained under fasting conditions by venipuncture in an antecubital vein and collected in plain tubes. After clotting, tubes were centrifuged and sera were kept at -80 °C until assayed. We measured serum 25(OH)D using the ARCHITECT 25-OH vitamin D chemiluminescent microparticle immunoassay (Abbott Diagnostics, Wiesbaden, Germany) [17]. Parathyroid hormone (PTH) was assayed with a chemiluminescent assay (PTH LIAISON N-TACT; DiaSorin, Saluggia, Italy). Serum calcium (Ca\(^{2+}\)) and phosphorus (P) levels were measured using a BM-Hitachi 747-200 autoanalyzer (Hitachi-Roche, Tokyo, Japan). Comparisons of biochemical parameters between the three subject groups were performed using ANOVA or Kruskal-Wallis tests, as appropriate. Serum concentrations of 25(OH)D were also dichotomized into 25(OH)D < 20 or \(\geq 20\) ng/mL, respectively, because this value has been previously shown to be a reliable cutoff for identifying subjects with greater disease risk [18]. Multivariate logistic regression analysis was performed to test the association between serum 25(OH)D < 20 ng/mL and EL and precocious AMI after adjustment for sex and CVD risk factors. The \(\alpha\) error was set at 0.05 (two-tailed).

We found significant differences in serum 25(OH)D levels among the three experimental groups, with centenarian ‘dodgers’ showing the highest 25(OH)D levels
followed by healthy young adults and AMI patients (Table 1 – see also Figure 1 for a box-and-whisker plots of serum 25(OH)D levels in the three study groups). All pairwise comparisons between the three study groups were significant (all \( p < 0.001 \)). There were no significant differences in PTH, \( Ca^{2+} \) or \( P \) concentrations among the groups. In multivariable analysis, the odds ratios for having serum 25(OH)D levels < 20 ng/mL was 0.31 (95% confidence interval (CI): 0.23, 0.77; \( p < 0.001 \)) in healthy centenarians and 3.85 (95% CI: 2.12, 6.79, \( p < 0.001 \)) in patients with precocious AMI.

Although the influence of potential environmental confounders (particularly, individual differences in sun exposure) cannot be ruled out, our data suggest that higher serum 25(OH)D levels are associated with healthy EL. Bischoff-Ferrari et al. [18] estimated the optimal serum concentrations of 25(OH)D in relation to bone mineral density, lower-extremity function, dental health, risk of falls, fractures, cancer prevention, incident hypertension and mortality. They concluded that 25(OH)D levels < 20 ng/mL are associated with adverse effects, while the ‘healthiest’ concentrations appeared to be close to 30 ng/mL. Of note, our centenarian dodgers showed mean serum 25(OH)D levels slightly higher than 30 mg/mL. In contrast, AMI patients’ mean levels were ~14 ng/mL, which falls in the range associated with higher likelihood of disease conditions. These authors also stated that an intake of vitamin D (cholecalciferol) \( \geq 40 \) \( \mu g \)/day is needed to reach at least 50% of the aforementioned 25(OH)D optimal concentrations [18]. Given the low incidence of malnutrition in Western countries, there is a small possibility that diet deficiencies play a role in the 25(OH)D differences observed in our study. Numerous risk factors have been associated with vitamin D deficiency, which should be ideally controlled for in future research. These include increased distance from the equator, shorter days related to non-summer seasons, indoor lifestyle, darkly pigmented skin, institutionalized/housebound, sunscreens and cover-up
clothing, air pollution, smoking, obesity, physical inactivity, genetic factors, malabsorption, renal and liver disease, and certain medications such as glucocorticoids, anti-rejection medications, human immunodeficiency virus medications, or some antiepileptic drugs [19].

In conclusion, serum vitamin D levels seem to be associated with successful aging, possibly reflecting, among other physiological advantages, a highly conserved cardiovascular function. The latter could play a central role in the extended life span of centenarians.

Conflict of interest: None declared.
References


[19] Lavie CJ, Lee JH, Milani RV. Vitamin D and cardiovascular disease will it live up to its hype? J Am Coll Cardiol 2011;58:1547-1556
Table 1. Serum levels of 25(OH)D, PTH, Ca\(^{2+}\) and P by group.

<table>
<thead>
<tr>
<th></th>
<th>Healthy adults (n=180)</th>
<th>Centenarian dodgers (n=79)</th>
<th>AMI patients (n=178)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D (ng/mL)</td>
<td>23.0 (13.3, 34.0)</td>
<td>32.1 (24.0, 34.2)*</td>
<td>14.4 (12.7, 23.1)*</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>39.1±14.6</td>
<td>41.7±19.1</td>
<td>43.7±17.2</td>
</tr>
<tr>
<td>Ca(^{2+}) (mg/dL)</td>
<td>9.4±0.5</td>
<td>9.5±0.5</td>
<td>9.4±0.4</td>
</tr>
<tr>
<td>P (mg/dL)</td>
<td>3.3±0.6</td>
<td>3.2±0.5</td>
<td>3.3±0.4</td>
</tr>
</tbody>
</table>

Data are expressed as medians (interquartile ranges) for skewed variables or means ± standard deviations for normally distributed data. Abbreviations: 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone; Ca\(^{2+}\), calcium; P, phosphorus. Symbol: *p<0.001 (All other p-values were not significant).
**Legend to Figure 1.** Box-and-whisker plots of serum 25-hydroxyvitamin D (25(OH)D) levels in the three study groups. The boxes represent the median (black middle line) limited by the 25th and 75th percentiles.