Vitamin D Levels for Preventing Acute Coronary Syndrome and Mortality: Evidence of a Nonlinear Association

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Context: Low serum calcidiol has been associated with multiple comorbidities and mortality but no "safe" range has been found for the upper concentration.

Objective: We aim to establish the upper threshold of serum calcidiol, beyond which there is an increased risk for acute coronary syndrome and/or mortality.

Design, Setting, and Participants: We extracted data for 1 282 822 Clalit Health Services members aged >45 between July 2007 and December 2011. Records of mortality or acute coronary syndrome were extracted during the follow-up period. Kaplan-Meier analysis calculated time to episode and Cox regression models generated adjusted hazard ratios for episode by calcidiol group (<10, 10.1–20, 20.1–36, and >36.1 ng/mL).

Outcome Measures: Acute coronary syndrome subsuming all-cause mortality.

Results: During the 54-month study period, 422 822 Clalit Health Services members were tested for calcidiol, of which 12 280 died of any cause (905 with acute coronary syndrome) and 3933 were diagnosed with acute coronary syndrome. Compared to those with 20–36 ng/mL, the adjusted hazard ratios among those with levels of <10, 10–20, and >36 ng/mL were 1.88 (confidence interval [CI]: 1.80–1.96), 1.25 (CI: 1.21–1.30), and 1.13 (CI: 1.04–1.22) ($P < .05$), respectively.

Limitations: The study cohort comprised only 30% of the population, those tested for vitamin D. The small sample size of those with calcidiol >36 ng/mL prevented further analysis of this group.

Conclusions: Vitamin D in the 20–36 ng/mL range was associated with the lowest risk for mortality and morbidity. The hazard ratio below and above this range increases significantly. **(*J Clin Endocrinol Metab* 98: 2160–2167, 2013)**

There is increasing evidence over the last several years of the pivotal role of vitamin D in human physiology. Evidence from multiple studies showed that low levels of serum calcidiol raise the risk of various morbidities (1–5) and confirmed the vital influence of vitamin D on human health with its direct involvement in more than 3000 genes (6) and indirect involvement in many others (7). There is also compelling evidence regarding the influence of low

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Abbreviations: BMI, body mass index; BP, blood pressure; CHS, Clalit Health Services; CI, confidence interval; HbA1C, glycosylated hemoglobin; HR, hazard ratios; IHD, ischemic heart disease; LDL, low-density lipoprotein; MACS, mortality or acute coronary syndrome; QC, quality control.

serum calcidiol on increased risk of cardiovascular events and mortality. Large-scale cohort studies and reviews (8–17) have found a 1.5-fold increase in mortality and cardiovascular events when comparing subjects with low vs moderate levels of serum calcidiol. A considerable increase in coronary artery stenosis was also shown among healthy elderly men and women with low serum calcidiol (<30 vs >30 ng/mL) (18). However, despite the remarkable influence on human health illustrated in many studies, calciol (D3 form) supplementation unexpectedly failed to decrease mortality, cardiovascular events, and other morbidities, whereas other studies found only minor positive effects (19–23). Prospective studies evaluating vitamin D supplementation are few and have not consistently shown benefit (24, 25). Such an unpredictable result may be due to the misconception that "the higher the better." In fact, in some studies, megavitamin D doses, 800-fold higher than the recommended daily allowance (26), were administered but did not improve the outcomes. It is therefore possible that only moderate supplementation within a narrow range of serum calcidiol will bear positive effects. Furthermore, supplementing the entire population may jeopardize those found within the upper normal range, shifting them to levels that are beyond the safe range.

In the current study we examined the safe limits of vitamin D blood levels and the cutoff points, below and above which the risk for mortality or acute coronary syndrome rises. More specifically, we investigated the existence of a possible U-shape association between vitamin D levels and the risk of the combined outcome, mortality, or acute coronary syndrome (MACS), hypothesizing that both low and high levels of vitamin D may increase the risk. We performed a large population-based historical prospective cohort study comprising more than 1 200 000 Clalit Health Services (CHS; Health Maintenance Organization) members, using the electronic health records. CHS members who were tested for vitamin D between 2007 and 2011 were included and the risk of MACS was examined by vitamin D levels, adjusting for a wide range of potential confounders.

Materials and Methods

Data and study population

CHS is the largest health care organization in Israel, insuring and providing care to over 4 million Israeli citizens (some 53% of the total population). CHS has an extensive and comprehensive integrated medical database, with over 10 years of electronic medical record data, facilitating rigorous large-scale studies. The data are compiled into a centralized warehouse where electronic health records are integrated from primary care and specialist clinics, hospitals, pharmacies, laboratories, as well as a chronic disease registry, containing chronic disease data gathered from all affiliated primary care physicians. CHS members' records are comprehensive, because they receive most care and treatments within CHS services, because data are also available for services received in non-CHS facilities, and because the annual CHS member attrition rate is generally below 1%.

We performed a historical prospective cohort study within the CHS population. All CHS members aged 45 and older, who had at least one recorded vitamin D blood test between July 2007 and December 2011 (54 mo), and who did not have a prior diagnosis of acute coronary syndrome before their calcidiol test, were included in the study population. Data were first extracted from the year 2007, as this was the year that testing rates greatly increased among the whole CHS population, corresponding to increased knowledge and interest on behalf of both the medical community and the public about the important role of vitamin D. We chose the time period of the study to increase the sensitivity of the study regarding the influence of both low as well as high concentrations of blood calcidiol on morbidity and mortality. The study was approved by the CHS Ethics Committee.

Laboratory methods

Biochemical analysis of blood was performed on fresh samples at CHS laboratories. These laboratories are authorized to perform tests according to the international quality standard ISO-9001. Periodic assessment of quality control (QC) is performed on a regular basis.

The accuracy of the measurements in the individual laboratory is confirmed by in-house daily QC monitoring and by monthly external QC program. 25-OHD was tested by the LIAISON 25-OH vitamin D TOTAL assay (27), a competitive 2-step chemiluminescence assay. The measuring range is 4 to 150 ng/mL (10–375 nM); the analytical sensitivity is <1.0 ng/mL, and the functional sensitivity is <4.0 ng/mL. The intra-assay coefficients of variation for low and high (7 and 130 ng/mL) calciol concentrations were 5.5% and 4.8% and the interassay coefficients of variation were 12.7% and 7.9%, respectively. Performance characteristics of the calcidiol assay were evaluated by the CHS laboratory and were comparable to the manufacturers' specifications.

Variables

Independent variables

The main predictor in our study was the first calcidiol level recorded during the study period, with values categorized into 4 groups (<10, 10–20, 20–36, and >36 ng/mL, approximately <25, 25–50, 50–90, and >90 nM, respectively). The demographic covariates assessed were age group (45–64, 65–84, and >85 y), gender, and population sector (general population, ultraorthodox Jews or Arab, determined at the clinic level). The 2 subgroups were targeted because they are assumed to be prone to insufficient serum calcidiol. Clinical covariates included were body mass index (BMI; <25, 25–30, and >30 kg/m^2), smoking status (never, former, or current), uncontrolled diabetes (glycosylated hemoglobin [HbA1C] groups <7, 7–9, >9), low-density lipoprotein (LDL) level (categorized as <100, ≥100), systolic blood pressure (BP; <140, 140–160, or >160), history of ischemic heart disease (IHD; see list of identifying codes in the supplemental data, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org), and season (winter, spring, summer, and fall).

Outcome

Acute coronary syndrome was based either on hospital diagnosis data or on a new diagnosis as postacute coronary syndrome at a physician's visit or from the CHS chronic disease registry. Acute coronary syndrome was defined according to the international classification list (ICD-9; see list of identifying codes in the supplemental data). In addition, all-cause deaths were retrieved from the Ministry of Interior reports. In Israel, 29% of deaths among this age group are attributed to cardiovascular diseases (28). We used a combined outcome in the study, both acute coronary syndrome and all-cause mortality, and referred to it here as MACS.

Statistical analysis

The distribution of the sociodemographic and clinical characteristics was examined across the 4 calcidiol level groups in the study population and in the general population. We also assessed the distribution of the characteristics across those with or without MACS and calculated the risk ratio, comparing the groups using χ^2. Survival analysis, Kaplan-Meier, and Cox proportional hazard regression were used to compare groups and estimate the hazard attributable to the combined outcome. Each participant was exposed from the time of the first calcidiol test and was right-censored on leaving CHS (a rare event) or at the end of the study period.

Kaplan-Meier survival curves were used to model the first occurrence of MACS between the first calcidiol assay and the end of the study period. Survival curves were generated for the 4 different calcidiol concentrations for each age group and for the general population. Groups were compared using the logrank test to determine equivalence between strata.

Cox proportional hazard multivariable models generated hazard ratios (HR) to examine the nonlinear association between MACS and calcidiol levels between July 1, 2007 and December 31, 2011, controlling for covariates that were significant in the univariate analyses ($P < .05$). A HR >1 is associated with an increased probability of MACS. The analysis was repeat stratified by gender. All statistical analyses were performed using SPSS software version 17.0 (SPSS Inc, Chicago, Illinois).

Results

Study cohort

There were 422 822 CHS members 45 years or older that were identified with at least one calcidiol blood test within the study period (33% of the CHS members aged 45+).

The study population disproportionally overrepresented the following groups as compared to the general CHS population: women, CHS members aged 65 to 84 (compared to the 2 other age groups), the ultraorthodox (compared to Arabs and the general population), members with normal BP, members with high LDL, and members with very high HbA1C (>9). Current smokers and overweight or obese subjects were less likely to have calcidiol tests. No difference in the populations was observed between members with and without IHD history. The median calcidiol level of the study population was less than 20 ng/mL (<50 nM) with 30% having serum calcidiol below 10 ng/mL; 32% with levels below 20 ng/ml; 35% with serum calcidiol between 20 to 36 ng/mL; and 3% with serum calcidiol above 36 ng/mL. Furthermore, calcidiol levels differed by winter, spring, summer, and autumn (17.6, 18.0, 20.7, and 19.8 mg/mL, respectively). Age groups were fairly evenly distributed across calcidiol levels; while women were more likely to have lower calcidiol levels than men, and the Arab and ultraorthodox populations were more likely to have lower levels than the general population. Nondiabetics had higher calcidiol levels, whereas persons with diabetes with HgbA1c >9 were more likely to have lower levels. Finally, those with the highest BMI were more likely to have lower calcidiol levels, whereas those in the normal BMI range were more likely to have higher levels (Table 1).

Calcidiol and MACS

During the study period, 16 213 MACS were recorded. Of these, 12 280 (75.7%) were deaths (905 with acute coronary syndrome) and 3933 (24.3%) were acute coronary syndrome. The univariate analysis found an inverse association between the incidence of MACS and calcidiol levels. The risk of MACS was positively associated with age; male gender; hypertension; uncontrolled diabetes; being a former smoker; having low LDL; having low BMI; and being part of the general population, as compared to the ultraorthodox or Arab-dominant clinics (Table 2). However, an age-adjusted analysis showed a greater risk of MACS for the younger Arab population, although not for ultraorthodox Jews.

Kaplan-Meier curves showed that calcidiol levels of 20 to 36 ng/mL were the most protective against MACS, compared to calcidiol levels of <10 ng/mL and were protective to a lesser degree compared to both the 10 to 20 ng/mL and >36 ng/mL levels, all differences being statistically significant (Figure 1). These findings were found across all age groups.

The Cox proportional hazard regression model, adjusted for all the relevant covariates (Table 3), confirmed that low levels of calcidiol (<20 ng/mL), as well as high levels (>36 ng/mL), were significant risk factors for MACS, when adjusted for all covariates. Compared to CHS members with calcidiol levels between 20 and 36 ng/mL, those with levels below 10 ng/mL had an HR of 1.91 (confidence interval [CI]: 1.83–2.00) and those with levels 10 to 20 ng/mL had an HR of 1.26 (CI: 1.22–1.31), whereas those with elevated serum calcidiol >36 ng/mL had an HR >1.13 (CI: 1.04–1.22) (Figure 2). Additional risk factors for MACS were being in the general population (as opposed to a minority group), having a history of

Table 1. Descriptive Statistics of the Study Population and General CHS

	Subjects With Calcidiol Test Serum Calcidiol, ng/mL[a]					
	<10	10–20	20–36	>36	All	All CHS Members
n (%)	70 338	170 554	165 152	16 778	422 822[b]	1 281 107[c]
Age						
45–64	57	56	54	51	55	61
65–84	36	39	42	44	40	34
>85	7	5	4	5	5	5
Sector						
General	67	87	94	95	87	86
Orthodox Jews	6	4	2	2	3	2
Arabs	27	9	4	3	10	12
Gender						
Males	23	31	34	36	31	46
Females	77	69	66	64	69	54
History of IHD						
No	96	95	95	94	95	95
Yes	4	5	5	6	5	5
Blood pressure						
<140	84	86	88	89	86	81
140–160	12	11	10	9	11	15
>160	4	3	2	2	3	4
LDL, mg/dL						
<100	37	37	41	49	39	34
>100	63	63	59	51	61	66
HgbA1C						
Nondiabetic	46	53	57	58	54	73
<7	38	36	35	36	36	19
7–9	11	8	6	5	8	6
>9	5	3	1	1	2	2
Smoking status						
Never	77	73	74	74	74	72
Former	9	13	13	14	12	9
Current	14	14	13	12	14	19
BMI						
<25	24	28	36	44	31	27
25–30	35	40	41	39	40	41
>30	41	32	23	17	29	32
Season						
Winter	30	23	19	18	23	—
Spring	30	25	22	21	25	—
Summer	19	26	32	34	27	—
Autumn	21	26	27	27	25	—

Dashes indicate not applicable.

[a] To convert to nmol/L, multiply by 2.5.

[b] After exclusion of 3 members.

[c] Comprises 61.5% of all Israeli population >45,2 043 000; estimated 98% are insured; all Israeli population (2007) 7 244 000.

IHD, having uncontrolled diabetes (according to HbA1C level), smoking, older age, male gender, and having high BP and low BMI. Furthermore, those with low vitamin D levels in the summer had a stronger positive association with MACS then those whose vitamin D was low in the winter.

A subdivision of the calcidiol concentration levels found that the range of 28 to 32 ng/mL was associated with the lowest risk of having a MACS event (Figure 2). This model was then stratified by gender (not displayed); the results for men and women were similar, although the relative risk of MACS among those with the lowest calcidiol levels (below 20 ng/mL), as compared to normal levels, was slightly greater among women. However, among those with the highest calcidiol levels, the relative risk for MACS was higher among men. The lowest HR for MACS was in the 20 to 36 ng/mL range for both genders.

Discussion

Just recently, Wang et al (15) described the influence of low levels of serum calcidiol on cardiovascular diseases

Table 2. Studied Population (Aged > 45) and Unadjusted Relative Risk of MACS

	MACS Events n (%)	All Study Population n (%)	Risk Ratio	*P* Value
Serum calcidiol, ng/mL				
<10	3833 (24)	70 338 (17)	1.71	<.0001
10–20	6420 (40)	170 554 (40)	1.18	<.0001
20–36	5278 (32)	165 152 (39)	1 (Reference)	
>36	682 (4)	16 778 (4)	1.27	<.0001
Age group				
45–64	2936 (18)	233 643 (55)	1 (Reference)	
65–84	9479 (58)	168 899 (40)	4.47	<.0001
>85	3798 (24)	20 280 (5)	14.9	<.0001
Sector				
General	14468 (89)	367 084 (87)	1 (Reference)	
Orthodox Jews	574 (4)	14 713 (3)	0.99	>.80
Arabs[a]	1171 (7)	41 025 (10)	0.72	<.0001
Gender				
Male	7297 (45)	131 681 (31)	1 (Reference)	
Female	8916 (55)	291 141 (69)	0.55	<.0001
History of IHD				
No	14140 (87)	402 831 (95)	0.34	<.0001
Yes	2073 (13)	19 991 (5)	1 (Reference)	
Blood pressure				
<140	12951 (80)	366 264 (87)	1 (Reference)	
140–160	2440 (15)	45 478 (11)	1.52	<.0001
>160	822 (5)	11 080 (3)	2.10	<.0001
LDL, mg/dL				
<100	8534 (53)	164 896 (39)	1 (Reference)	
>100	7679 (47)	257 926 (61)	0.58	<.0001
HgbA1C				
Nondiabetic	6751 (42)	226 928 (54)	1 (Reference)	
<7	6616 (41)	152 102 (36)	1.46	<.0001
7–9	2156 (13)	33 538 (8)	2.16	<.0001
>9	690 (4)	10 254 (2)	2.26	<.0001
Smoking status				
Never	11545 (71)	312 099 (74)	1 (Reference)	
Former	2663 (16)	52 586 (12)	1.37	<.0001
Current	2005 (12)	58 137 (14)	0.93	<.0001
BMI				
<25	5528 (34)	131 218 (31)	1 (Reference)	
25–30	6137 (38)	167 123 (40)	0.87	<.0001
>30	4548 (28)	124 481 (29)	0.87	<.0001

[a] An age-adjusted analysis of the population sectors shows greater risk of MACS for Arabs but not for ultraorthodox Jews compared to the general population.

and mortality. However, very few studies included in their review examined the influence of higher levels of vitamin D on these outcomes and thus were unable to define the upper safe limits of calcidiol blood levels. In our large comprehensive database of CHS, we have determined the safe range of calcidiol blood levels and suggested a threshold for excess vitamin D, beyond which CHS members are at increased risk for MACS (all-cause mortality and/or cardiovascular events). We defined a safe range of serum calcidiol of 20 to 36 ng/mL (50 to 90 nM) and found a U-shape association of the risk for MACS and serum calcidiol. This finding is also corroborated by other studies, which describe a similar range, centered around 25 to 40 ng/mL (1, 29–35). This safe range also applies to all-cause mortality; in the MACS outcome, 24% of the events were due to acute coronary syndrome, whereas 76% pertained to all-cause mortality.

Our findings also corroborated the expected association between typical risk factors (and potential confounders), such as age, gender, IHD history, hypertension, serum cholesterol, diabetes, smoking, and BMI, and the risk of MACS (Table 2). Although each risk factor bears an independent risk by itself, none of them obscured the U-shape correlation effect of serum calcidiol on MACS.

Furthermore, only about 35% of the tested CHS members fell into the safe vitamin D range, which is further corroborated by other studies (9–16, 36). Remarkably, about 3% of our CHS members who had high levels of serum calcidiol had an elevated risk of MACS compared to the safe range. According to the vitamin D response

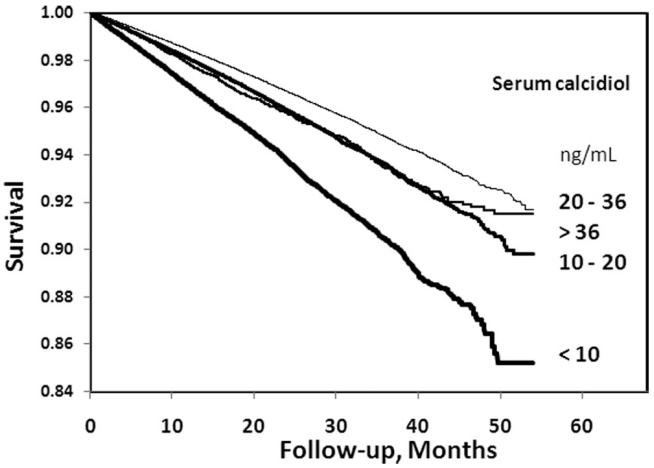

Figure 1. Kaplan-Meier survival curves by serum calcidiol. Follow-up of MACS events (16213) in 422822 subjects (aged >45 over 54 months), for four ranges of serum calcidiol (<10 ng/mL, 10–20, 20–36, >36). The curve for the highest serum calcidiol level lies significantly below that of the 20–36 level.

curve, a daily supplementation of calciol at a range of 1600 to 2400 IU, which is commonly indicated, might raise the serum calcidiol of most of the population beyond the safe serum range, greater than 36 ng/mL (90 nM) (37).

Our study has certain limitations. Because of the relatively small number of CHS members with high serum calcidiol, we could not further subdivide higher levels of serum calcidiol (>36 ng/mL) to assess for their impact on risk of MACS. In addition, our study sample of members with vitamin D tests comprises only 30% of the total CHS population aged 45 and older, and thus the study sample may be biased (sicker, more health conscious, more educated, or urban-dwellers). Furthermore, women were tested for serum calcidiol at a rate nearly twice that of men. This is not surprising, because women tend to visit their family doctors more. Compared to other studies, the duration of our study (54 mo) may be too short to capture acute coronary syndrome and mortality events related to vitamin D blood levels adequately. We also have not considered seasonal fluctuations of about 17% around the average (38). Finally, individual polymorphic effects may affect the optimal serum calcidiol, which may require personalized targets.

In conclusion, we identified a safe target range of 20 to 36 ng/mL for serum calcidiol, which minimizes the risk for acute coronary syndrome and all-cause mortality, during a 54-month time period. The U-shaped association has been corroborated by other large-scale studies when looking at the relationship between vitamin D and all-cause mortality, cardiovascular events, and cancer (1, 8, 14, 29–36, 39).

A 12-year prospective cohort in the United States showed that those with vitamin D >30 ng/mL had a higher HR than those with 20 to 29 ng/mL (Figure 1A) and found

Table 3. Multivariate Analysis of the Hazard Ratio for MACS Among the Studied Population

	β (SE)	Hazard Ratio [95% CI]	*P* Value
Serum calcidiol, ng/mL			
<10	0.63 (0.02)	1.91 (1.83–2.00)	<.001
10–20	0.23 (0.02)	1.26 (1.22–1.31)	<.001
20–36		1 (Reference)	
>36	0.12 (0.04)	1.13 (1.04–1.22)	<.003
Age group			
45–64		1 (Reference)	
65–84	1.31 (0.02)	3.71 (3.55–3.87)	<.001
>85	2.61 (0.03)	13.6 (12.9–14.3)	<.001
Sector			
General		1 (Reference)	
Orthodox Jews	−0.07 (0.04)	0.94 (0.86–1.00)	.118
Arabs	−0.06 (0.03)	0.94 (0.86–1.02)	.066
Gender			
Female		1 (Reference)	
Male	0.58 (0.02)	1.79 (1.73–1.85)	<.001
History of IHD			
No		1 (Reference)	
Yes	0.48 (0.02)	1.61 (1.54–1.69)	<.001
Blood pressure			
<140		1 (Reference)	
140–160	0.07 (0.02)	1.07 (1.02–1.12)	<.003
>160	0.24 (0.04)	1.27 (1.18–1.36)	<.001
LDL, mg/dL			
<100		1 (Reference)	
>100	−0.14 (0.02)	0.87 (0.83–0.91)	<.001
HgbA1C			
Nondiabetic		1 (Reference)	
<7	0.22 (0.02)	1.24 (1.20–1.28)	<.001
7–9	0.53 (0.03)	1.70 (1.61–1.79)	<.001
>9	0.86 (0.04)	2.36 (2.17–2.55)	<.001
Smoking status			
Never		1 (Reference)	
Former	0.10 (0.02)	1.10 (1.06–1.15)	<.001
Current	0.34 (0.03)	1.40 (1.34–1.47)	<.001
BMI			
<25		1 (Reference)	<.001
25–30	−0.22 (0.02)	0.80 (0.77–0.83)	<.001
>30	−0.14 (0.02)	0.87 (0.83–0.91)	
Season			
Winter		1 (Reference)	
Spring	−0.023 (0.02)	0.98 (0.94–1.02)	.30
Summer	0.070 (0.02)	1.07 (1.03–1.12)	<.002
Autumn	0.08 (0.02)	1.08 (1.04–1.1)	<.001

evidence of a U-shape association during the follow-up period. Furthermore, the odds ratio of >2.3 associated with high serum levels of calcidiol for acute coronary syndrome described by Zitterman et al (36) further supports the burden and the risk of high calcidiol concentrations.

Other studies also found an increased risk of falling in older individuals at the highest serum calcidiol concentrations (40, 41). Consequently, we maintain that our findings are sound enough to promote public recommendations for optimal serum calcidiol and calciol (D3 form) supplementation. We suggest that this safe target range for serum calcidiol, which is considered the surrogate marker

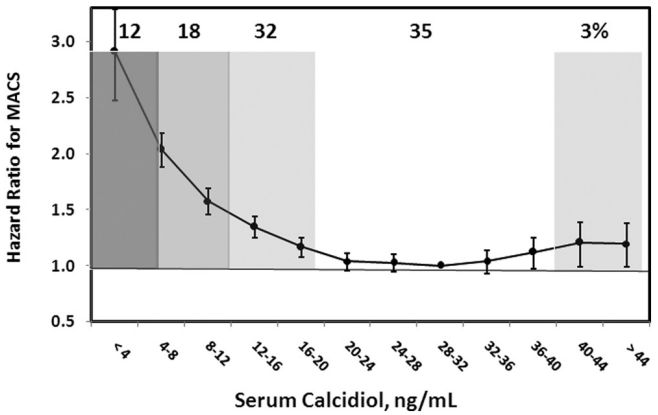

Figure 2. Adjusted hazard ratio for MACS by serum calcidiol. Calcidiol assays were tested in 422822 subjects (aged >45), while 16213 had MACS events within 54 months. The population percentage for each range of serum calcidiol is shown at the top of the graph. Only 35% of the subjects lay within the safe range (20–36 ng/mL). At risk are 62% of the subjects who fall below the safe range with hazard ratios of MACS >1.26 and another 3% who are above the safe range with hazard ratios of 1.13. Error bars represents 95% CIs.

for vitamin D status, will guide health authorities in optimizing calciol supplementation.

The reason for a U-shape correlation between calcidiol blood concentration and all-cause mortality and cardiovascular morbidity, which we found in our study, is unclear. Vitamin D regulates the activity of more than 3000 different genes and there are at least 5 distinct forms of this vitamin or more (42) in the circulation. These different forms are also affected by numerous enzymatic activities, which are controlled by an unknown number of microRNA (43). The main activity of vitamin D is attributed to the absorption of calcium. This may explain our observation that high concentrations of this vitamin accelerate coronary calcification, an assumption that was also suggested by multiple other studies. However, it seems that calcitriol intervenes in more than one hundred different biological functions and, at present, we do not have sound biological evidence regarding the mode of operation of vitamin D and in particular the deleterious effect of high concentrations.

Practical approach

In view of our findings, as well as similar findings of several other studies, we suggest a conservative approach regarding the recommendations for vitamin D supplementation, to reduce the risk of jeopardizing the segment of the population who is already at the upper limit of the safe range of blood levels of calcidiol. The amount of supplementation needs to be tailored specifically to individuals based on the range their vitamin D blood level falls into (ie, for subjects with serum calcidiol levels of 20 ng/mL, supplementation of 30 μg/d [1200 IU] might suffice to attain serum calcidiol of 32 ng/mL, while those whose blood level is 30 ng/mL may require only 5 μg/d [200 IU], which would raise their serum calciol to a level of 32 ng/mL, which is still in the safe range). Because of the wide polymorphism effect, occasional measurements of circular calciol are suggested (44).

Acknowledgments

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