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Importance of Tracking, Season, Sunny Vacations and Supplementation for Clinical Evaluation of Serum 25-Hydroxyvitamin D Levels

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Abstract

Objective: There has been a huge increase in numbers of serum 25-hydroxyvitamin D (25OHD) measurements in spite of uncertainty concerning the benefits of vitamin D supplementation, uncertainty about what is a sufficient serum 25OHD level and how to interpret serum 25OHD measurements.

Methods: 255 subjects who participated in a 5-years intervention study with vitamin D for the prevention of type 2 diabetes and who were allocated to placebo were included. Serum 25OHD levels were measured annually, and questionnaires on sunny vacations and vitamin D supplementation filled in.

Results: The serum 25OHD levels were ~ 20 nmol/L higher in the summer than the winter months; those taking vitamin D supplements had ~ 5 nmol/L higher 25OHD levels than those not taking supplements; a recent sunny vacation increased the serum 25OHD levels 8-16 nmol/L; and there was a high degree of tracking of serum 25OHD with correlation coefficient (r) between baseline and the following annual measurements between 0.67 and 0.75.

Conclusions: If considering a serum 25OHD level of 50 nmol/L as sufficient and that this level should be attained year-round, and taking season, vitamin D supplementation status and recent sunny vacation into account, a single measurement will in most situations be reliable and sufficient for making clinical decisions without need for numerous repeat measurements.

Keywords: Season; Sun exposure; Supplementation; Tracking; Vitamin D

Introduction

Vitamin D is produced in the skin after sun exposure or is acquired through the diet or by vitamin supplements [1]. Vitamin D is essential in calcium metabolism, and may be important for prevention of cancer, cardio-vascular, infectious and immunological diseases [2]. Although intervention studies with vitamin D in general have been disappointing [3], the number of serum 25-hydroxyvitamin D (25OHD) measurements for evaluation of the vitamin D status, as well as the use of vitamin D supplements, have increased manifold during the last decade.

There is no general agreement on what is an optimal serum 25OHD level, but a level of 50 nmol/L is generally considered as sufficient [4]. However, as the 25OHD level is influenced by sun exposure, a summer or winter measurement may not give equivalent information, and recent sunny holidays may also have considerable effects. Furthermore, there are no guidelines concerning whether or when there is a need for follow-up measurements, and accordingly, the interpretation of a single measurement may be difficult.

To elucidate these factors one should ideally follow a large group of subjects over time with repeated serum 25OHD measurements from all seasons combined with registration of changes in life-style factors, sunny holidays and vitamin D supplements. We have recently performed a five years intervention study with vitamin D in 511 subjects, of whom 255 subjects were allocated to placebo. The subjects were followed closely regarding factors known to affect the serum 25OHD level, which was also measured annually. We therefore had the opportunity to address some of the questions regarding how to interpret a random serum 25OHD measurement.

Methods

Design

The design of the study, which had prevention of type 2 diabetes (T2D) with vitamin D supplementation as primary endpoint, has been described in detail previously [5]. In short, the subjects were principally recruited from the sixth survey in The Tromsø Study 2007-2008, where 4393 subjects with HbA_{1c} in the range 5.8–6.9% and not previously diagnosed diabetes were invited to an oral glucose tolerance test (OGTT). Among the 3476 that completed the OGTT, 713 men and women age 25-80 years had impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) [6] and were invited to participate in the present study, of which 511 were included. Subjects with primary hyperparathyroidism, granulomatous disease, history of urolithiasis, cancer diagnosed in the past 5 years, unstable angina pectoris, myocardial infarction or stroke in the past year were excluded. Pregnant or lactating women, or women of fertile age with no use of contraception, were not included.

All visits were performed at the Clinical Research Unit at the University Hospital of North Norway. The subjects were randomized (non-stratified) in a 1:1 ratio to one capsule vitamin D (cholecalciferol 20,000 IU (Dekristol; Mibe, Jena, Germany)) per week or an identical looking placebo capsule containing arachis oil (Hasco-Lek, Wroclaw, Poland). For the next five years the subjects met annually for new OGTT and blood sampling. At all visits questionnaires on vitamin D supplementation and sunny vacation were filled in. Sunny vacation was defined as having been in a Mediterranean country (or similar) during the months May-September or in a tropical country (any time of the year) for a least one week. The subjects were instructed not to take vitamin D supplements (including cod liver oil) exceeding 400 IU per day during the study.

If at the annual OGTT the fasting blood glucose was >6.9 mmol/L and/or the 2-h value >11.0 mmol/L and/or HbA_{1c} was ≥ 6.5% the subject was considered to have T2DM, thus ending their participation in the study, and thereafter retested (if necessary) and followed by their general practitioner. In the initial protocol, subjects who during the study were diagnosed with cancer, coronary infarction, unstable angina pectoris, or stroke, were to be excluded from the study. From October 2011 this was changed to exclusion of subjects who during the study developed serious disease making it difficult or impossible to attend scheduled visits.

Measurements

Routine biochemical analyses were performed as previously described [6]. Serum concentrations of 25(OH)D were measured by in-house liquid chromatography–tandem mass spectrometry method that detects both $25(OH)D_3$ and $25(OH)D_2$ and the sum of these presented as 25(OH)D in the results [7].

Statistical analyses

Distribution was evaluated with visual inspection of histograms and by kurtosis and skewness and found normal for the relevant variables. Correlations were evaluated with Pearson's correlation coefficient (r), and comparisons between groups were performed with Student's t-test. A multiple regression model was used to evaluate predictors for change in serum 25OHD with age, sex, baseline serum 25OHD, change from baseline in vitamin D supplementation status and recent sunny vacation status, and delta BMI as covariates.

P<0.05 (two-tailed) was considered statically significant. Data are presented as mean ± SD. All statistical analyses were performed using IBM SPSS version 22 software (SPSS INC, Chicago, Illinois, USA). Power calculation was performed for the primary endpoint (prevention of T2D) only, and not for the present analysis.

Ethics

The study was approved by the Regional committee for Medical Research Ethics (REK NORD 81/2007) and by the Norwegian Medicines Agency (2007-002167-27).

Results

Baseline results

A total of 511 subjects were included in the intervention study. Two hundred and fifty-five subjects were allocated to placebo and are included in the present study.

Their baseline characteristics are shown in Table 1. The subjects taking vitamin D supplementation had ~ 5 nmol/L higher serum 25OHD levels than those not taking supplements (P=0.08). Subjects who had been on a sunny vacation for at least one week the last two months (recent sunny vacation) had ~ 8 nmol/L higher serum 25OHD levels (P=0.003) than those who had been on such a vacation 2–12 months ago, and ~ 16 nmol/L higher serum 25OHD levels (P=0.007) than those who had not been on sunny vacation the last year. These differences were particularly seen during the winter months.

All subjects (n=255)	
Males/females	153/102
Age (years)	61.9 ± 9.2
BMI (kg/m^2)	29.8 ± 4.4
Serum 25(OH)D (nmol/L)	62.4 ± 21.3
Serum calcium (mmol/L)	2.31 ± 0.08
Serum creatinine (umol/L)	69.5 ± 13.9
Serum ASAT (U/L)	30.9 ± 37.2
Hemoglobin (g/dL)	14.4 ± 1.2
Serum PTH (pmol/L)	5.6 ± 2.2
Subjects taking vitamin D supplementation[1] (n=92) Serum 25(OH)D (nmol/L)	65.5 ± 18.9
Subjects not taking vitamin D supplementation1 (n=163) Serum 25(OH)D (nmol/L)	60.7 ± 22.4
Subjects been on sunny vacation[2] last 2 months	
Summer[3] (n=14), serum 25(OH)D (nmol/L)	73.6 ± 22.1
Winter[4] (n=16), serum 25(OH)D (nmol/L)	73.2 ± 18.3
Subjects been on sunny vacation[2] 2-12 months ago	
Summer[3] (n=42), serum 25(OH)D (nmol/L)	75.0 ± 24.4
Winter[4] (n=49), serum 25(OH)D (nmol/L)	57.6 ± 13.8
Subjects not been on sunny vacation[2] last year	
Summer[3] (n=65), serum 25(OH)D (nmol/L)	63.2 ± 21.6
Winter[4] (n=69), serum 25(OH)D (nmol/L)	52.8 ± 18.5

Table 1: Baseline characteristics of the 255 subjects. [1]Including cod liver oil; [2]Vacation for at least one week in tropical area year round or the Mediterranean (or equivalent) May-September; [3]Sample drawn May-September; [4]Sample drawn October-April.

As shown in Figure 1 (where only the subjects who had not been on a recent sunny vacation are included) the baseline serum 25OHD levels were 15-25 nmol/L higher in the summer (May–September) than the winter months (October–April), a difference that was similar also in the measurements at the 1, 2, 3, 4 and 5 year visits (data not shown).

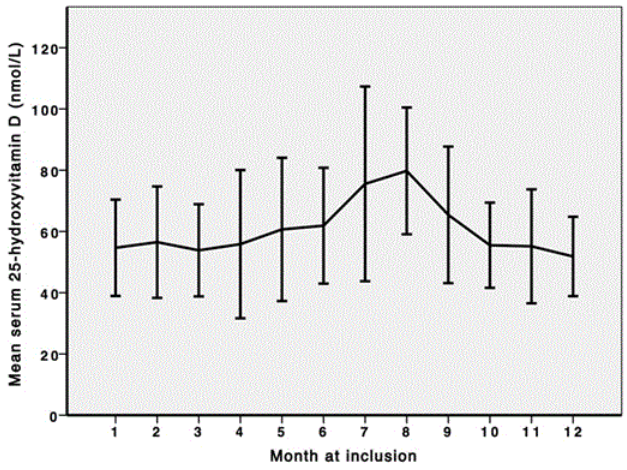

Figure 1: Mean serum 25-hydroxyvitamin D at baseline in the 225 subjects who had not been on a recent (last two months) sunny vacation in relation to month of blood sampling (1=January, 2=February etc.)

Tracking

Before the final 5-year visit, 99 subjects had developed T2D and 45 had dropped out for various reasons [5]. Thus, 241 attended the 1-year visit, 187 the 2-year visit, 161 the 3-year visit, 133 the 4-year visit and 111 the 5-year visit.

There was a high degree of correlation between the annual serum 25OHD measurements as shown in Table 2, with correlation coefficient r being 0.67–0.85 (P<0.001). In comparison, the correlation coefficients between baseline and 1-year for BMI, serum calcium, serum creatinine, serum ASAT, serum PTH and haemoglobin were 0.95, 0.49, 0.85, 0.48, 0.84 and 0.76, respectively. The high degree of correlation between annual serum 25OHD measurements was seen in those having their visits during the summer months as well as in those having their visits during the winter months (data not shown), and was further increased if only including those who had similar sunny vacation exposure and vitamin D supplementation status prior to the visit (Supplemental Table 1).

		1 year visit	2 year visit	3 year visit	4 year visit	5 year visit
Baseline	r	0.71	0.70	0.75	0.67	0.69
	n	241	187	161	133	111
1-year visit	r	-	0.70	0.72	0.69	0.62
	n	-	187	161	133	111
2-year visit	r	-	-	0.76	0.74	0.76
	n	-	-	161	133	111
3-year visit	r	-	-	-	0.79	0.79
	n	-	-	-	133	111
4-year visit	r	-	-	-	-	0.85
	n	-	-	-	-	111

Table 2: Correlations between the annual serum 25OHD measurements. All correlations P<0.01.

The magnitude of change in serum 25OHD level from baseline till the 1-year visit is illustrated in Figure 2 and Table 3. Thus, among the 122 subjects with serum 25OHD>60 nmol/L at baseline, only 7 (5.7%) had serum 25OHD<50 nmoL/L at 1-year, and among the 31 subjects with serum 25OHD <40 nmol/L at baseline, only 7 (22.6%) has serum 25OHD>50 nmolL/L at 1-year visit. This high degree of tracking persisted throughout the study as shown for changes from baseline to the 5-year visit (Supplementary Table 2).

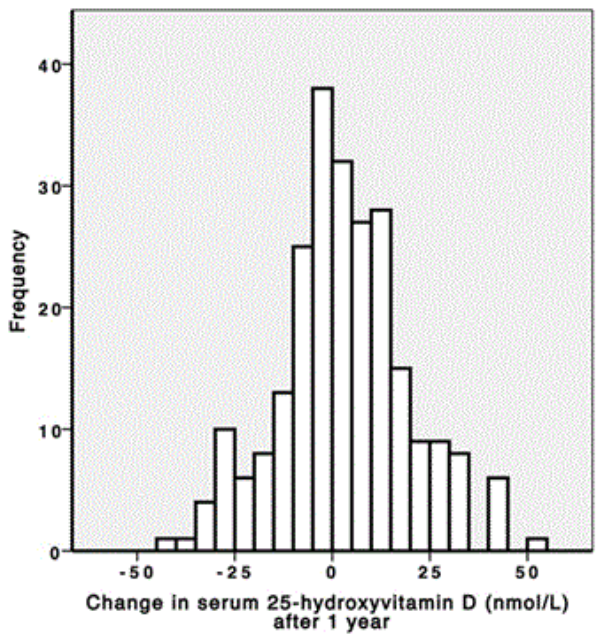

Figure 2: Change in serum 25-hydroxyvitamin D from baseline (value after 1-year minus value at baseline) in the 241 subjects who met at the 1-year visit.

Predictors of change in serum 25OHD levels

In a multiple linear regression model with delta 25OHD (value at 5 years minus value at baseline) as the dependent variable, the baseline serum 25OHD level and change in recent sunny vacation status were significantly associated with delta 25OHD, change in vitamin D supplementation status was borderline significant (P=0.058), whereas age, sex and change in BMI were not significantly associated with delta 25OHD (Supplemental Table 3).

This influence of sunny vacation on change in mean serum 25OHD as compared to baseline is shown in Table 4, where subjects who had not been on a sunny vacation at baseline but at an annual visit, had a 6–15 nmol/L increase in mean serum 25OHD level, whereas in the reverse situation, there was a mean decrease of 0.3–8.8 nmoL/L. For change in vitamin D supplementation status the changes were smaller (<5 nmol/L) and non-significant (data not shown).

Baseline serum 25OHD groups, nmol/L	1-year serum 25OHD groups, nmol/L						
	<30	30-39	40-49	50-59	60 - 69	>69	n
<30	2	4	0	0	0	0	6
30-39	0	8	10	4	3	0	25
40-49	0	6	17	12	0	4	39
50-59	0	1	9	20	13	6	49
60-69	0	2	2	6	9	21	40
>69	0	0	3	4	15	60	82
n	2	21	41	46	40	91	241

Table 3: Number of subjects in serum 25OHD groups after 1 year in relation to serum 25OHD group at baseline.

Sunny vacation as compared to baseline		n	Delta serum 25OHD (serum 25OHD at respective visit minus serum 25OHD at baseline)
1 year visit	Recent sunny vacation at baseline, but not now	24	-7.1 ± 16.6
	Same as baseline	205	3.3 ± 16.1
	Recent sunny vacation now, but not at baseline	12	14.6 ± 15.6***
2 year visit	Recent sunny vacation at baseline, but not now	17	-5.1 ± 12.3
	Same as baseline	155	-1.4 ± 14.7
	Recent sunny vacation now, but not at baseline	14	10.0 ± 27.2*
3 year visit	Recent sunny vacation at baseline, but not now	14	-0.3 ± 13.5
	Same as baseline	136	0.6 ± 14.7
	Recent sunny vacation now, but not at baseline	11	15.3 ± 11.6*
4 year visit	Recent sunny vacation at baseline, but not now	14	-6.9 ± 12.2
	Same as baseline	101	0.1 ± 16.0
	Recent sunny vacation now, but not at baseline	18	6.1 ± 17.6
5 year visit	Recent sunny vacation at baseline, but not now	10	-8.8 ± 14.3

	Same as baseline	93	3.1 ± 14.8
	Recent sunny vacation now, but not at baseline	8	13.5 ± 17.8**

Table 4: Delta serum 25OHD (value at annual visit minus value at baseline) in relation to change in recent sunny vacation status from baseline till later annual visits. *P<0.05, *P<0.01, ***P<0.001 versus Recent sunny vacation at baseline, but not now.

Discussion

In the present study we have found a high degree of tracking for serum 25OHD that persisted for at least five years, and also demonstrated the importance of season as well as previous sunny vacation for evaluation of serum 25OHD levels.

The high degree of tracking for serum 25OHD has been demonstrated in several previous studies [8-12]. Most studies have included only two time points, and correlation coefficients have ranged from 0.4 to 0.8 depending on experimental design, time span between measurements and whether follow-up samples were drawn at same seasons. With the possible exception of adolescence [13], this tracking pattern has been reported in practically all age groups.

This long term stability of the serum 25OHD levels has been taken as an argument for the use of single 25OHD measurements for prediction of later events in epidemiological research [8], but is also important in a clinical setting. Thus, for a subject with a serum 25OHD level above 69 nmol/L, it is highly unlikely that the level will be below 50 nmol/L if measured a year later, and similarly, if the level is below 30 nmol/L, it is even more unlikely that it will increase to above 50 nmol/L the next year.

However, in spite of a considerable degree of tracking, interpretation of serum 25OHD levels is not straight forward. First of all, there is no general consensus on what is a sufficient or optimal serum 25OHD level. According to the Endocrine Society, a serum 25OHD level of 75 nmol/L or above is recommended [14], whereas the Institute of Medicine (IOM) found no proven additional benefit of increasing serum 25OHD above 50 nmol/L [4]. Even if using the IOM cut-off there are still ~ 40% of Europeans that will be classified as vitamin D deficient [15]. Furthermore, the guidelines do not fully take seasonal variation into account, in particular whether the serum 25OHD should be >50 nmol/L year-round or if it is enough if 25OHD is above this level most of the year.

This is a topic that has not received much attention, and is of course difficult to answer. However, if there is a causal relation between vitamin D deficiency and all the diseases where an observational association has been found [2], then it is logical that the serum 25OHD should be above 50 nmol/L year-round.

Although large, longitudinal studies with serum samples drawn repeatedly throughout the year in the same subjects are lacking, it is reasonable to assume that in most individuals the serum 25OHD levels are 20 nmol/L higher in the summer than the winter, and accordingly, a level of <70 nmol/L in the summer indicates that the subject will be deficient during the winter. In this regard, it should be noted that large differences between summer and winter values are not only seen at higher latitudes, but worldwide including countries in southern Europe [16].

In addition to season, we also found a pronounced effect of a recent sunny holiday, in particular during the winter season. Thus, if the serum 25OHD is measured in a subject with a recent sunny vacation during the winter, and one wants to use this value to predict the serum 25OHD level the rest of the year, one should probably subtract close to 20 nmol/L from this measurement.

Similarly, the vitamin D supplementation status of the subject should be taken into account. In a recent review on effects of vitamin D supplementation it was noted that for similar doses the reported increases in 25OHD differed up to fourfold between trials, with an average increase of 2 nmol/L per 1 ug (40 IU) of vitamin D given [17]. If so, then the difference between subject with and without vitamin D supplementation (of at least 400 IU per day) should be as high as 20 nmol/L which was not seen in our present study nor in our previous epidemiological studies [18]. This probably reflects a much higher compliance in clinical trials than in clinical practice. Therefore, from a practical point of view, if a subject reporting use of vitamin D supplementation in the range of 400–800 IU per day stops taking these supplements, one can probably expect a reduction in serum 25OHD levels of 5–10 nmol/L.

In addition to season, sunny vacations and supplements, the serum 25OHD level is of course influenced by the diet, in particular by intake of fatty fish, and also by body weight [19]. We found no significant effect of change in BMI in our study, probably because the BMI changes in this cohort were modest, and dietary changes were not recorded. The study also has several other shortcomings; the subjects included all had IGT or IFG, they were not allowed to take vitamin D supplementation exceeding 400 IU per day which could mask effects of stopping such supplements, and the use of solarium, which could have a substantial effect on the serum 25OHD levels [20], was not recorded. On the other hand, we included a large group of subjects and followed them repeatedly over a five years period.

In recent years there has been a great focus on vitamin D deficiency [21], and the number of serum 25OHD measurements in clinical practice have increased dramatically. However, it should be emphasized that we, except for prevention of rickets and osteomalacia, currently do not know the benefits of vitamin D supplementation. Hopefully this will be settled when we have the results of the large the on-going vitamin D intervention trials, like the the ViDA study in New Zealand with 5110 participants and the VITAL study in the US with 25875 participants with results expected within 3–5 years [22]. Until then, measurement of serum 25OHD should not be done as screening, but on clinical suspicion of deficiency. If evaluated with caution and taking season, sunny vacation and vitamin D supplementation status into account, a single measurement will in most situations be reliable and sufficient for making clinical decisions without need for numerous repeat measurements.

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