



Seasonal variation in vitamin D levels in the Canterbury, New Zealand population in relation to available UV radiation

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Abstract

Aim The optimal plasma 25-hydroxyvitamin D (25(OH)D) concentration is probably >75 nmol/L but in temperate regions lower levels are common. Few studies report the intensity of solar ultraviolet (UV) radiation when 25(OH)D is measured. We measured plasma 25(OH)D and incident solar UVB radiation in Christchurch and modelled the relationship between them.

Methods 25(OH)D, total calcium (Ca_T), ionised calcium (Ca_I) and parathyroid hormone (PTH) were measured in healthy volunteers (119 female, 82 male; median age 45 years, range 18 to 83) between February and July 2004. Vitamin D-weighted UV energy measurements (dUV) for Christchurch were from the National Institute of Water and Atmospheric Research (NIWA) UV Atlas.

Results In February 2004, 88% of 25(OH)D levels were below 75 nmol/L, increasing to 100% in June and July. Severe deficiency (<12.5 nmol/L) was found in 1.5% of subjects. From February to July, 25(OH)D and Ca_I fell and Ca_T rose ($p < 0.001$, < 0.01 , and < 0.001). There was a hyperbolic relationship between PTH and 25(OH)D while Ca_T and Ca_I correlated negatively with PTH ($r = -0.30$ and -0.33 ; both $p < 0.001$). Monthly mean dUV intensity ranged from $10 \text{ kJ} \cdot \text{m}^{-2} \cdot \text{day}^{-1}$ in Dec 2003 to $0.5 \text{ kJ} \cdot \text{m}^{-2} \cdot \text{day}^{-1}$ in June 2004. Compartmental modelling estimated that a Christchurch person made 1200 IU/day of vitamin D in mid-summer but only 60 IU/day in midwinter. Daily supplements of 1450 or 2600 IU vitamin D₃ are predicted to raise the annual minimum mean plasma 25(OH)D to 75 or 100 nmol/L respectively.

Conclusions Most Christchurch people are vitamin D deficient most of the time and a daily supplement of 2600 IU vitamin D₃ would correct this.

It is recommended by some authorities that the plasma concentration of 25-hydroxyvitamin D₃ [25(OH)D] should be at least 75 nmol/L.¹⁻³ This figure is based both on observational evidence relating 25(OH)D levels to the risks of fracture, periodontal disease, colorectal cancer, and lower-extremity muscle weakness, and on the 25(OH)D levels found in those, such as farmers and lifeguards, with sun exposure typical of conditions in which modern skin tones evolved.

Further, a randomised controlled 4-year study of cholecalciferol plus calcium supplementation in postmenopausal women, which raised plasma 25(OH)D from 72 to 96 nmol/L, reduced by 77% the likelihood of being diagnosed with cancer between 1 and 4 years after the initiation of the trial.⁴

In contrast, surveys, especially of older people, even in apparently sunny countries such as Spain, Italy and Greece,⁵ Brazil,⁶ and Australia,⁷ show high proportions of people with 25(OH)D levels less than 75 nmol/L, particularly during winter months.

Within New Zealand, a survey of the Auckland workforce found that a large proportion of the workers, if not the majority, had serum 25(OH)D concentrations below 75 nmol/L,⁸ as did Auckland elderly,⁹ pregnant women in Wellington,¹⁰ Dunedin elderly,¹¹ and New Zealand children throughout the country.¹²

In a survey of New Zealanders aged 15 years and older, 3% were considered to have frank deficiency (<18 nmol/L) and 48% insufficiency, based on a cut-off of 50 nmol/L,¹³ and with differences apparent due to age, gender, latitude, and season.

Only a few studies at a limited number of latitudes (23°S,⁶ 37°S,⁹ and 68°N¹⁴) have measured the intensity of ultraviolet radiation (UV) at ground level at the same time as the 25(OH)D measurements were made. The studies at 23°S and 37°S were limited to older subjects (>40 years and >65 years respectively) and the study at 68°N had only 15 participants and covered a time period of only 60 days.

We now report the relationship between plasma 25(OH)D levels and solar UV in the general adult population in a southerly New Zealand location. We also develop a model of vitamin D metabolism to assist in the effective remediation of poor vitamin D status.

Methods

Subjects

Volunteer group—The subjects were residents of Christchurch, New Zealand (44°S), who volunteered to participate in a study to establish reference intervals for endocrine and metabolic test methods. The study was approved by the Upper South B Regional Ethics Committee. Recruitment was performed by contacting individuals selected randomly from Christchurch electoral rolls (241 responses, a 14% response rate) or by advertising (76 responses).

Volunteers completed a health questionnaire and were accepted if aged 18 or over, considered themselves healthy, and did not meet exclusion criteria that included diabetes and endocrine conditions, relevant cancers, steroid medication and recent hospitalisation. Of the initial volunteers, 33% were excluded either to meet study criteria or to avoid a more severe gender imbalance.

A single morning blood sample was collected within the period of February to August 2004 from 209 individuals of whom 105 were fasting. After further excluding those who were taking vitamin D supplements or cod-liver oil, 25(OH)D measurements were available for 201 volunteers (119 females, 82 males).

The mean (\pm SD) age was 46 \pm 14 years with a median of 45 years (range 18 to 83) and the mean (\pm SD) body mass index was 26.3 \pm 4.7.

Patient group—This group consisted of patients within the Christchurch region from whom samples were submitted to Canterbury Health Laboratories for measurement of plasma 25(OH)D between 1 July 2003 and 31 December 2004.

3702 samples were from females and 1138 from males, with a mean (\pm SD) age of the whole group of 59 \pm 23 years and a median age of 63 years (range 0.1 to 101). Samples were submitted from hospital wards, outpatient clinics and private practices. It is not known how many patients were taking vitamin D supplements.

Biochemical analyses

25(OH)D was measured using the DiaSorin radioimmunoassay kit (Stillwater, MN, USA). The antibody cross-reacts with vitamin D₂ and D₃ equally and results are the mean of duplicate determinations with internal and external QC samples in each batch. The low, medium, and high QC

values with coefficients of variation are 16.5 (16.2%), 35.9 (7.8%), and 132 (7.8%) nmol/L respectively. The laboratory is a participant in the DEQUAS (Charing Cross Hospital, London, UK) vitamin D external quality control programme.

Plasma calcium was measured on the Abbott Aeroset analyser (Abbott Laboratories, Abbott park, IL, USA) by colorimetry using the Arsenazo-III dye method with correction for albumin (+ 0.02*[40 – albumin(g/L)]). The intra-assay CV was 0.8% at 3 mmol/L.

Serum ionised calcium was measured on the Corning C865 blood gas analyser (Ciba Corning Diagnostic; Medfield, MA, USA) by calcium ion-selective electrode (between-batch CV 1% at 1.22 mmol/L). Assay stability was assured, as a matter of routine, by collation of daily patient means for all major analytes on the Abbott Aeroset analyser and by collation of monthly means and SDs for all internal QC samples. No significant assay drift was evident for either calcium or albumin over the time period of the study.

Parathyroid hormone (PTH) and C-telopeptide (CTX) were measured using the Roche Elecsys 2010 system. The low, medium, and high QC values with coefficients of variation are 2.2 (6.9%), 8.2 (5.3%), and 31.5 (4.7%) pmol/L for PTH—and 0.46 (7.5%), 0.59 (10.4%), and 1.64 (5.2%) µg/L for CTX.

Bone-specific alkaline phosphatase (BALP) was measured using the Beckman ACCESS system and the low and high QC values with coefficients of variation are 10.9 (7.5%) and 64.2 (6.8%) µg/L.

UV radiation

Daily UV irradiances (W/m^2) at 1-hour intervals were taken from the National Institute of Water and Atmospheric Research (NIWA) UV Atlas software package (<http://www.niwascience.co.nz/services/uvozone/atlas>).

The irradiances for Christchurch were summed to give the mean for each month of total erythemally-weighted UV (eUV) and vitamin D-weighted UV (dUV) per day. For erythema, the weighting is according to McKinlay and Diffey.¹⁵ For vitamin D, the weighting is from Maclaughlin Anderson and Holick,¹⁶ normalised to unity at 315 nm and truncated at 315 nm as suggested by MF Holick (personal communication, 2006).

The data product is derived from a combination of short-wave pyranometer data to estimate cloud effects, satellite-derived estimates of ozone, and a radiative transfer model.¹⁷ The pyranometer data are from LICOR LI-200 sensors. The accuracy is approximately $\pm 10\%$.

The UV data in the current study is the environmentally available UV. This study did not attempt to measure or estimate personal UV exposure, which depends on an individual's lifestyle, and may be only 3% or less of that available.¹⁸

Statistical analysis

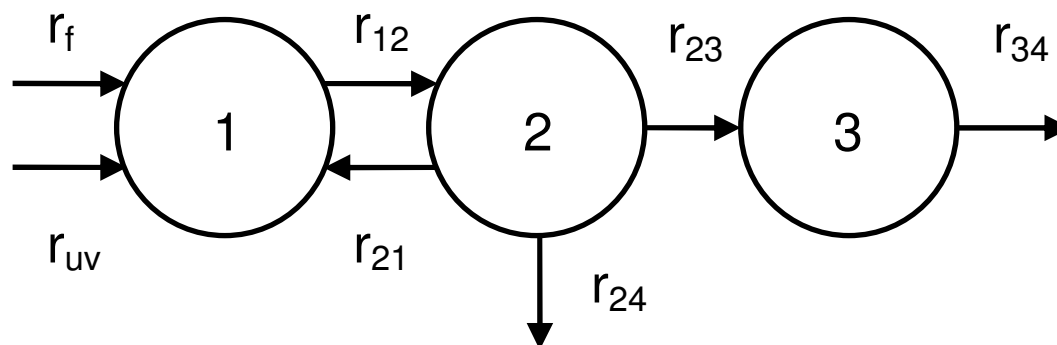
The NCSS statistical package (Kaysville, Utah, USA) was used for analyses. Confidence intervals (CI) for estimates are 95% intervals. Correlations were calculated by the non-parametric Spearman procedure and a significance level of 0.01 was used in view of the number of correlations examined.

Modelling

We used the three-compartment model of vitamin D metabolism shown in Figure 1 to represent the production and losses of vitamin D₃ and 25(OH)D in humans.

Compartments 1 and 2 are, respectively, faster and slower turnover vitamin D₃ compartments while compartment 3 contains 25(OH)D. Parameter v_3 , the volume of the 25(OH)D compartment, was taken to be 8 litres,¹⁹ and the half-life of 25(OH)D was taken to be about 10 days,²⁰ giving a value for k_{34} of 0.5. The other parameters in the model are: v_1 , v_2 , the volumes of compartments 1 and 2; r_f , the dietary intake of vitamin D; k_{uv} , the rate constant for cutaneous vitamin D production by solar dUV; rate constants k_{12} and k_{21} representing the interchange of vitamin D between compartments 1 and 2; k_{23} , the rate of conversion of vitamin D to 25(OH)D; k_{24} , the rate of metabolism of vitamin D by other pathways; and k_{34} , the rate of conversion of 25(OH)D to other metabolites. The parameters α and β define the non-linear feedback control of k_{23} by the concentration of 25(OH)D.

Figure 1. Model of vitamin D metabolism



Compartment 1 and 2 contain vitamin D₃ and compartment 3 contains 25(OH)D; 4 denotes further (undefined) metabolites. Rates (nmol/day) are denoted r and rate constants k . Parameters α and β define the feedback of 25(OH)D on its production rate. r_f =dietary vitamin D₃, $r_{uv}=k_{uv}E_{uv}$, E_{uv} =dUV energy, $r_{12}=k_{12}c_1$, $r_{21}=k_{21}c_2$, $r_{24}=k_{24}c_2$, $r_{23}=k_{23}c_2=c_2\alpha/(1+\beta c_3)$, $r_{34}=k_{34}c_3$.

To obtain values for the parameters in the model, the best-fit values for v_1 , v_2 , k_{12} , k_{21} , α , β , k_{24} , and k_{34} were estimated from the data taken from the literature given in Table 1 using the downhill simplex optimisation procedure.²¹ Then, to estimate the quantitative relationship between UVB radiation in Christchurch and the plasma 25(OH)D levels in the volunteer group, best-fit estimates of r_f and k_{uv} were obtained by fitting the model to the mean monthly 25(OH)D values in the volunteer group and the daily dUV energy intensity measurements during 2003 and 2004. The goodness-of-fit criterion was the minimum absolute deviation.

Table 1. Data from the literature used to estimate the parameters of the model in Figure 1

Dosage	Reference	Datum	Units	Observed value	Predicted value
300000 IU D ₃ oral bolus	Wu et al ²²	25(OH)D, maximum	day	17	22
		Δ 25(OH)D, maximum	nmol/L	65	77
		Δ 25(OH)D, 100 days	nmol/L	38	37
50000 IU D ₃ oral bolus	Armas et al ²³	Δ D3, 1 day	nmol/L	30	31
		Δ D3, 3 days	nmol/L	12	12
		25(OH)D, maximum	day	15	23
		Δ 25(OH)D, maximum	nmol/L	17	18
10000 IU D ₃ daily	Heaney et al ²⁴	Δ 25(OH)D, 21 days	nmol/L	63	44
		Δ 25(OH)D, 130 days	nmol/L	152	148

Values predicted by best-fit model parameter values also shown.

Results

The results for plasma 25(OH)D are summarised in the upper two panels of Figure 2. Plasma 25(OH)D tended to rise as UVB energy rose in spring and to fall as UVB energy fell in autumn. For the individual values in the volunteer group, the amplitude of a sine function fitted to 25(OH)D was 17.3 nmol/L (CI=12.1 to 22.6, n=201), and

for the monthly mean 25(OH)D in the patient group was 8.4 nmol/L (CI=4.5–12.2, n=17).

The 25(OH)D levels tended to lag behind UVB and for both subject groups the Spearman correlation between dUV and 25(OH)D was at a maximum when the lag was 2 months, being 0.89 (n=6, p=0.02) for the volunteer group and 0.79 (n=16, p<0.001) for the patient group.

There was no significant difference in the monthly mean 25(OH)D levels between females and males in the volunteer group (mean difference=0.5 nmol/L, CI =-4.4–5.3 nmol/L, n=6)—but in the patient group, monthly mean 25(OH)D levels were higher for females (mean difference=2.9 nmol/L, CI=0.5–5.3 nmol/L, n=18).

Table 2 gives the proportions of subjects in the volunteer group with 25(OH)D levels below commonly used^{9,10} cut-off levels. The large majority had below optimal levels (<75 nmol/L) regardless of the time of year and the majority showed insufficiency (<50 nmol/L) in June, July, and August.

Deficiency (<25 nmol/L) was evident in at least a few individuals in each month studied and rose to 35% of the volunteer group in July-August. Only 1.5% of the volunteers had 25(OH)D below 12.5nmol/L (1 person in May and 2 in July).

Table 2. Monthly proportions of the volunteer subject group with plasma 25(OH)D concentrations below specified levels

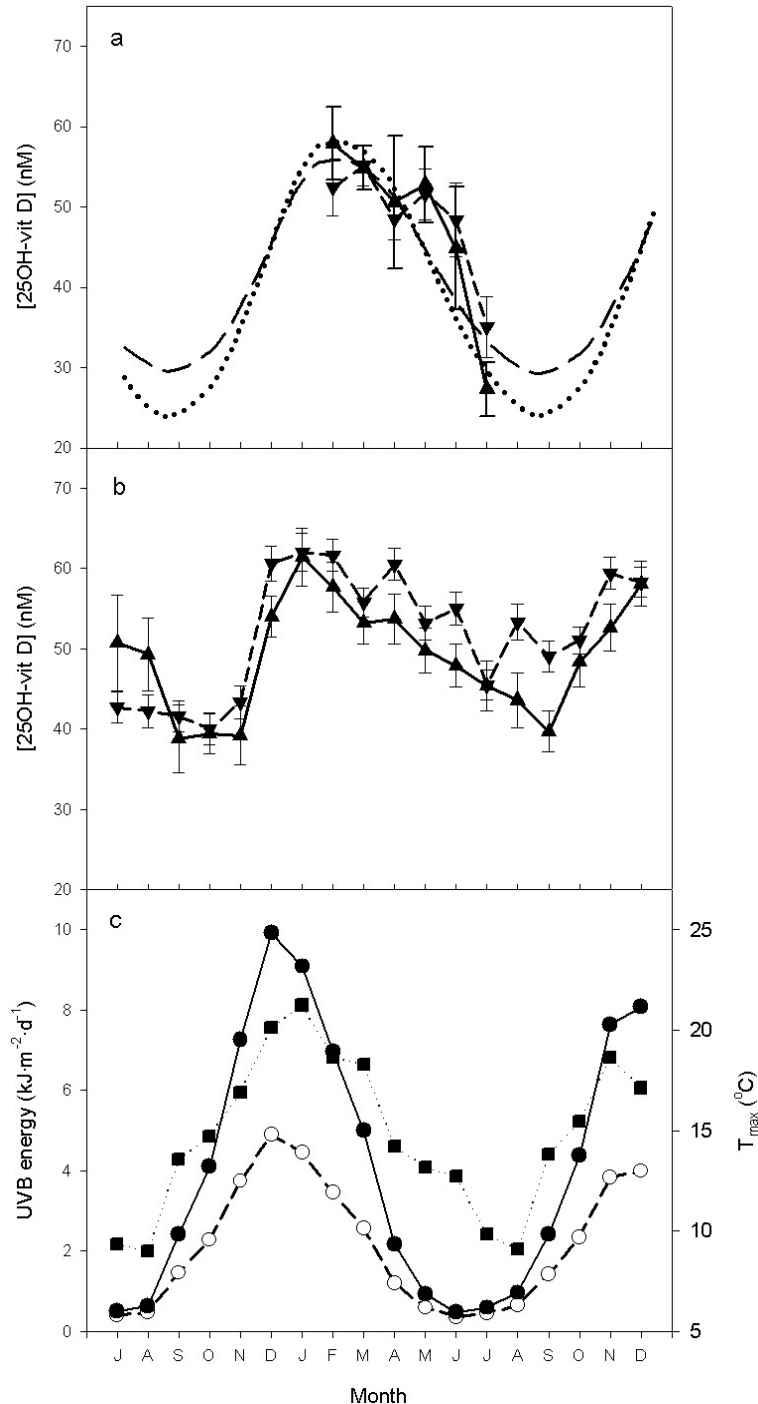
Month	Number of subjects	<25 nM (%)	<50 nM (%)	<75 nM (%)
February	40	3	40	88
March	63	2	40	91
April	28	7	39	93
May	35	3	46	91
June	11	9	64	100
July–August	26	35	89	100

The correlations between the time of year and the measured analytes, and between the analytes, are given in Table 3 for the volunteer group. As the year progressed 25(OH)D levels fell (p<0.001), total calcium (Ca_{tot}) rose (p<0.001), and ionised calcium (Ca⁺⁺) fell (p<0.01). PTH levels were neither significantly correlated with time of year nor with 25(OH)D levels but for the non-linear regression function, PTH=a + b/25(OH)D, the estimates of a and b (with CI) were 2.83 (2.51–3.15) and 24.4 (12.7–36.1).

The mean±SEM February (n=40) and July/August (n=25) values for total calcium were 2.20±0.02 and 2.28±0.02 mmol/L respectively. The corresponding values for ionised calcium were 1.19±0.01 mmol/L and 1.14±0.01 mmol/L.

The monthly ratios of mean daily dUV and eUV energies in Christchurch are shown in Figure 3.

Figure 2. Monthly plasma 25-hydroxy vitamin D concentrations in male and female Christchurch residents (mean±SEM) for (a) the volunteer group and (b) the patient group; (c) represents the corresponding monthly means of the UVB energy received daily at ground level and the maximum daily temperature. The first month is July 2003 and the last month is December 2004.



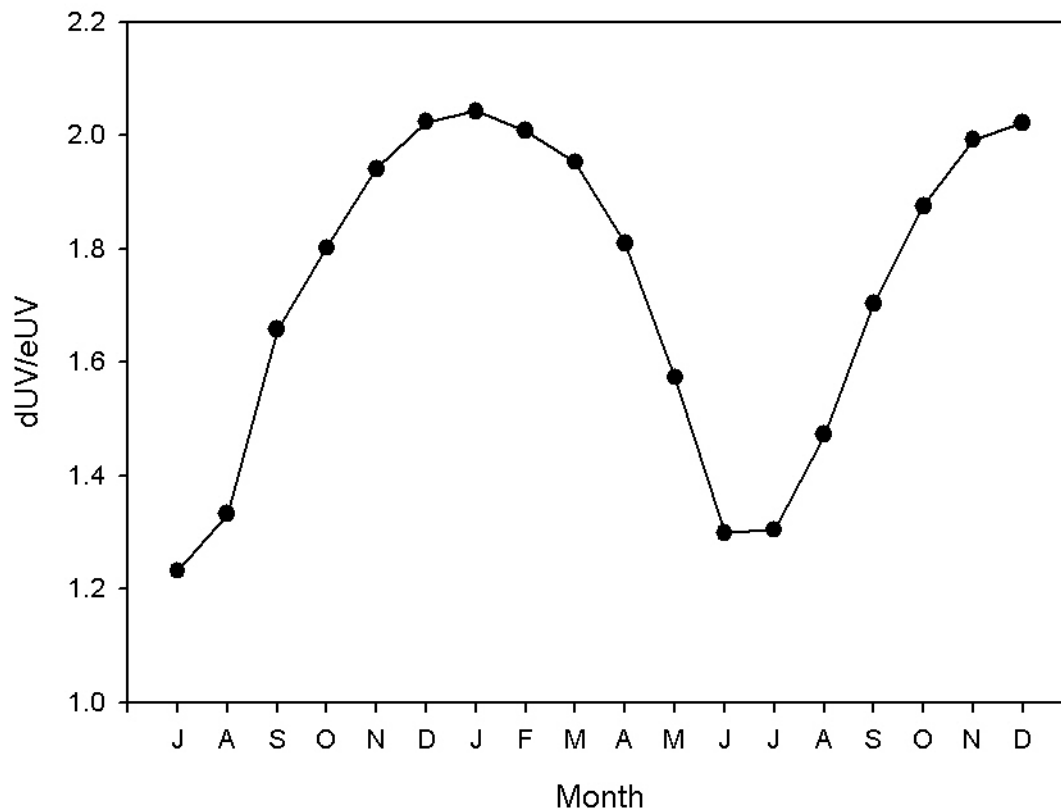
In (a) and (b), \blacktriangle — \blacktriangle male, \blacktriangledown — \blacktriangledown female. The smooth dashed line in (a) is the prediction of the best-fit model (dietary vitamin D 350 IU/d), and the dotted line shows the best fit if dietary vitamin D is assumed to be 200 IU/d. In (c), \bullet — \bullet dUV, \circ — \circ eUV, \blacksquare — \blacksquare maximum temperature. The one volunteer studied in August (with a 25(OH)D value of 22 nmol/L) is not included.

Table 3. Correlations within the volunteer group

Variables	Time	25(OH)D	PTH	BALP	CTX
25(OH)D	-0.30**	1			
PTH	-0.16	-0.10	1		
BALP	-0.01	-0.21*	0.20*	1	
CTX	-0.10	-0.13	0.33**	0.45**	1
Ca _{tot}	0.37**	-0.08	-0.30**	0.03	-0.07
Ca ⁺⁺	-0.19*	0.21*	-0.33**	-0.02	0.00

* p<0.01, **p<0.001; PTH=Parathyroid hormone; BALP=bone-specific alkaline phosphatase; CTX=C-telopeptide.

Figure 3. Ratio of mean daily vitamin D-weighted UV energy (dUV) to mean daily erythemally-weighted UV energy (eUV) in Christchurch monthly from July 2003 to December 2004



The best-fit values of the parameters for the model of vitamin D metabolism are given in Table 4. The estimated dietary intake of vitamin D (r_f) is 23 nmoles/day (9 µg/day or 350 IU/day) and k_{uv} is estimated to be 8 nmol·m²·kJ⁻¹. The predicted values for the literature-derived data using the best-fit parameters are given in Table 1.

The plasma 25(OH)D concentrations predicted for the volunteer group throughout 2004 are shown in Figure 2a, both for the best-fit dietary vitamin D intake of 350 IU/d, and for an assumed dietary intake of 200 IU/d, in which case the best-fit value of k_{uv} is $10 \text{ nmol}\cdot\text{m}^2\cdot\text{kJ}^{-1}$.

Table 4. Best-fit estimates of the parameters of the model of vitamin D metabolism

Parameter	Value	Units
v_1	53	litre
v_2	60	litre
v_3	8^\dagger	litre
r_f	23	$\text{nmol}\cdot\text{day}^{-1}$
k_{uv}	8.0	$\text{nmol}\cdot\text{m}^2\cdot\text{kJ}^{-1}$
k_{12}	39	$\text{litre}\cdot\text{day}^{-1}$
k_{21}	6.9	$\text{litre}\cdot\text{day}^{-1}$
k_{24}	0.81	$\text{litre}\cdot\text{day}^{-1}$
k_{34}	0.5^\dagger	$\text{litre}\cdot\text{day}^{-1}$
α	1.33	$\text{nmol}\cdot\text{day}^{-1}$
β	0.039	$\text{litre}\cdot\text{nmol}^{-1}$

† Values obtained directly from literature.

The quantity of supplemental vitamin D needed to raise the modelled annual minimum mean plasma 25(OH)D in the volunteer group to 75 nmol/L is predicted to be 1450 IU/d ($36\mu\text{g}/\text{d}$), or to raise the annual minimum mean to 100 nmol/L, 2600 IU/d ($64\mu\text{g}/\text{d}$). In the latter case, the annual maximum mean plasma 25(OH)D is predicted to be 114 nmol/L. For both simulated supplement doses the annual maximum mean plasma 25(OH)D occurred in mid February and the annual minimum mean in early September.

In the absence of sunlight, the corresponding supplementation required is predicted to be 1600 IU/d ($41\mu\text{g}/\text{d}$) and 2700 IU/d ($68\mu\text{g}/\text{d}$). On the other hand, if year-round sunlight exposure were to be doubled, in the absence of supplementation, the annual maximum plasma 25(OH)D is predicted to rise from 56 nmol/L to 80 nmol/L and the annual minimum to rise from 29 nmol/L to 37 nmol/L.

Discussion

The two principal findings of this study are firstly that most, if not all, of the apparently healthy general population in Christchurch do have not adequate circulating levels of 25(OH)D at some time during the year, and secondly that relatively high levels of supplementation with vitamin D would be required to achieve healthy concentrations of 25(OH)D year round.

Considering first the high prevalence of vitamin D deficiency, Table 2 shows that even in summer, in February, only 12% of the volunteer group had optimal (>75 nmol/L) plasma 25(OH)D levels. This percentage fell during the autumn and winter until in June, July, and August, no one achieved this level.

Of even greater concern is that in every month studied, at least some of these self-declared “healthy” people were vitamin D deficient (<25 nmol/L). By July-August this proportion reached 35%.

The situation appears to be little better in the patient group where the average monthly levels of plasma 25(OH)D ranged from 40–62 nmol/L. This is despite it being likely that many of this group were on vitamin D supplementation and were having their 25(OH)D measured to check the dose level (Simon Wynn-Thomas, personal communication, 2007). Evidently few of this group would have maintained a level of 25(OH)D of at least 75 nmol/L year round.

These findings raise the question of what could be done about the near universal state of vitamin D deficiency in Christchurch, particularly in winter. Supplementation with vitamin D₃ is probably the most practical possible remedy on account of its ease of administration, safety,²⁵ and cost effectiveness. The novel modelling done in this paper is designed to give a guide to the necessary dosage levels and is the first description of a model of vitamin D metabolism that includes solar radiation.

The model suggests that taking 1450 IU of vitamin D₃ per day, in addition to normal sun exposure and dietary intake, would maintain the average 25(OH)D levels in healthy Christchurch people at 75 nmol/L or above all year. However many would still fall below 75 nmol/L at some time, so an annual minimum average of 100 nmol/L is probably more desirable and this is predicted to require a supplement of 2600 IU per day.

In New Zealand, prescription vitamin D₃ is only available as 50000 IU (1.25 mg) tablets (Cal.D.Forte[®]), hence 2600 IU/d is approximately equivalent to 1 tablet every 19 days, or approximately 2 per month. This is considerably greater than the dose rate recommended in the Medsafe datasheet (<http://www.medsafe.govt.nz/Profs/Datasheet/c/CalDFortetab.htm>) of 1600 IU/d (1 tablet per month), but well below the 10000 IU per day which has recently been suggested as no-observed-adverse-effect level.²⁵ However safety data from large studies and beyond 5 years is lacking.

Our finding that supplemental vitamin D₃ of about 1450 IU/d would be required to raise minimum average levels of 25(OH)D to 75 nmol/L is comparable to the 1700 IU/d that Vieth and coworkers¹ estimate to be required to raise levels from 50 nmol/L to 80 nmol/L, and so suggests our model is plausible.

Another strategy for raising 25(OH)D levels might be greater personal exposure to solar dUV, although this is not without risk as excessive UVB exposure can result in skin and eye damage.

Could the risk be minimised by choosing conditions where the ratio of vitamin D production to erythema is maximal? As can be seen from Figure 3, the vitamin D produced from a given erythemal exposure is greater in summer than at other times of year. This is because the sun is higher in the sky and hence the shorter wavelength dUV is less attenuated by the atmosphere compared to the attenuation of the longer wavelength eUV. Similarly, sun exposure at midday is preferable to exposure earlier or later in the day if the aim is to maximise vitamin D production while minimising burning.

However, we would not recommend a vitamin maintenance strategy based on midday summer sun for three reasons. Firstly, in summer it can take as little as 15 minutes to cause sunburn in sensitive individuals. Secondly, low levels of 25(OH)D are primarily a wintertime problem—but, as vitamin D in the body has a relatively short half-life of about 90 days,²² summer production would be of limited effectiveness by late winter. Thirdly, because the skin has some ability to repair UV damage, the same total dose received over a longer period, say weeks, results in less (or no) burning, compared to the same dose received in a shorter period, say 30 minutes.

Our estimate of $8 \text{ nmol}\cdot\text{m}^2\cdot\text{kJ}^{-1}$ for the rate constant for production of vitamin D by dUV (k_{uv} , Table 4) for a presumably typical person in Christchurch, allows the estimate that on an average day in midsummer when dUV energy is say 10 kJ/m^2 , that person gains 1200 IU/d of vitamin D from their solar exposure. In contrast, in midwinter, when average daily dUV is probably about 0.5 kJ/m^2 , only about 60 IU would be made.

Since the amount of solar exposure our subjects had was not measured, we cannot estimate the absolute amount of additional solar exposure that would be needed to raise 25(OH)D levels to at least 75 nmol/L year round. However our modelling prediction that doubling average solar exposure year-round would only raise the average minimum 25(OH)D by 8 nmol/L suggests that it would probably be impossible to raise the annual minimum to 75 nmol/L by increasing sun exposure in Christchurch.

Hence this leaves vitamin D supplementation as the only practical measure for usefully raising the annual minimum plasma 25(OH)D level. Note that doubling solar exposure does not double 25(OH)D levels, and the non-linearity between dUV exposure and plasma 25(OH)D is also evident between summer and winter when dUV varies by about ten-fold but 25(OH)D by about two-fold.

A similar study to the present one was conducted in Auckland, New Zealand, at about the same time (January 2004 to May 2005).⁹ There, the monthly mean plasma 25(OH)D levels in women were a little higher (maximum 63 nmol/L in March, minimum 40 nmol/L in August) than in Christchurch, but the mean levels found in men were markedly higher (maximum 102 nmol/L in March and minimum 59 nmol/L in September).

The generally higher 25(OH)D levels in Auckland no doubt reflect its lower latitude (37°) but it is not clear why the men were found to have much higher levels than the women, particularly as we did not find a significant gender difference in Christchurch in the volunteer group and, if anything, a reverse gender difference in the patient group (Figure 2).

Our observation of no significant negative correlation between PTH levels and 25(OH)D may be because very few (1.5%) of the volunteer group had severe vitamin D deficiency ($25(\text{OH})\text{D} < 12.5 \text{ nmol/L}$). However when parametric statistics rather than non-parametric were used, a non-linear hyperbolic relationship was evident.

Our three compartment model of vitamin D metabolism (Figure 1) is based on the two compartment model proposed and used by Heaney and coworkers,²⁴ but with two additions. One addition is a rapid turnover vitamin D compartment (compartment 1) in order to account for plasma measurements of vitamin D_3 ,²³ and the other addition is

that the rate of conversion of vitamin D to 25(OH)D, r_{23} , is under feedback control by 25(OH)D. This is to account for observations suggesting that the increase in plasma 25(OH)D is not linear with increasing dose of vitamin D, but tends to lessen with larger doses.²⁶

The assumption that this non-linearity is due to feedback by 25(OH)D is largely speculative, since another possibility is that the 25-hydroxylase enzymes in the liver tend to become saturated by larger quantities of vitamin D. However preliminary manipulation of our model suggested that the former assumption provided a better fit to the data in Table 1 than did the latter possibility (data not shown). Note that our model is a pragmatic mathematical construct designed to describe the plasma measurements in a way that allows predictions to be made; it is not intended that the compartments correspond to definite physiological or anatomical entities.

There is no straightforward way to estimate the uncertainties in the parameter estimates for the model (Table 4) because different assays for 25(OH)D can give differing values, the uncertainty of some of the data in Table 1 is unknown, and the parameter optimisation algorithm does not lend itself to error estimation. In addition, different experimenters can obtain quite different estimates for ostensibly the same parameter, for example the slope of the relationship between vitamin D₃ dose and plasma 25(OH)D increment.²⁶

The limited number of months for which we measured 25(OH)D levels in the volunteer group limits the precision of the estimates of the values of the model parameters k_{uv} and r_f . As the estimate of 350 IU/d for vitamin D intake from food (and from visits to sunnier places), r_f , might be considered high, k_{uv} was also estimated on the assumption that r_f was 200 IU/d. This gave a value of k_{uv} that was only 25% higher, suggesting that the best-fit estimate of k_{uv} is reasonably robust. However, we have not been able to allow for the probably greater exposure of skin to the sun in the warmer months.

Studies are underway to improve the seasonal range of measurements, to directly measure personal exposure to solar UV and to quantify the relationship between personal UV exposure and vitamin D status. The measurement of actual personal exposure to UV is critical and will be novel and challenging.

It should be noted that our model, and its predictions regarding dosages to raise 25(OH)D levels, apply only to vitamin D₃ since Heaney's group²³ have shown that vitamin D₂ is metabolised much more rapidly and does not raise or maintain plasma 25(OH)D levels as effectively.

In summary, our study finds firstly, as many others¹ have, that residents in temperate regions have unhealthily poor vitamin D status, and secondly, that modelling suggests that vitamin D supplementation in greater than the usually recommended dosage is required to address the problem.

Competing interests: Drs Florkowski and Elder are employees of Canterbury Health Laboratories, which might benefit commercially if there is an increased interest in testing vitamin D levels in patients upon this paper's publication (although this paper does not explicitly advocate testing vitamin D status).

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