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Changes in vitamin-D metabolites and parathyroid hormone in plasma following cholecalciferol administration to pre- and postmenopausal women in the Netherlands in early spring and to postmenopausal women in Curaçao

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To study the effect on plasma 25-hydroxycholecalciferol (25(OH)D), 1,25-dihydroxycholecalciferol ($1,25(OH)_2D$) and parathyroid hormone (PTH) we supplemented premenopausal (aged 30 (SD 7) years) and postmenopausal (aged 61 (SD 2) years) white women living in The Netherlands in late winter/early spring, and elderly black and white women (aged 75 (SD 6) years) living in Curaçao (Dutch Antilles) with either 10 or 20 μg cholecalciferol/d for 4, 5 and 9 weeks respectively. Baseline plasma 25(OH)D concentration of Dutch women was lower than that of Curaçao women. Postmenopausal Dutch women had a higher PTH concentration in plasma than premenopausal Dutch and postmenopausal Curaçao women. There were no differences in plasma $1,25(OH)_2D$. Cholecalciferol administration increased 25(OH)D in all groups, $1,25(OH)_2D$ in postmenopausal Curaçao women and PTH in postmenopausal Curaçao women and premenopausal Dutch women. Serum and urinary Ca and phosphate concentrations did not change. There were no response differences between 10 and 20 μg doses. Oral cholecalciferol administration (either 10 or 20 μg/d) to women living at northern latitudes in late winter/early spring increased 25(OH)D levels to the baseline levels of elderly people living in the tropics.

Cholecalciferol: Parathyroid hormone: Osteoporosis

Vitamin-D deficiency is rare among people living in tropical climates as long as they regularly expose themselves to sunlight. We recently reported (Dubbelman *et al.* 1993; Jonxis *et al.* 1993) higher 25-hydroxycholecalciferol (25(OH)D) and somewhat higher 1,25-dihydroxycholecalciferol ($1,25(OH)_2D$) plasma levels in postmenopausal white women living in the tropics (Curaçao, The Netherlands Antilles; 12·15° north latitude), compared with counterparts living at more northerly latitudes (The Netherlands; 52° north). (In the present paper, for the sake of simplicity, women living in The Netherlands and Curaçao are

* Professor Jonxis died on 26 July 1995.
† For reprints.

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described as 'Dutch' and 'Curaçao' women respectively, although all of them have Dutch nationality.) Vertebral compression fractures commonly encountered in postmenopausal white women living at higher latitudes were absent in Curaçao counterparts. These differences may be explained by the abundant sunlight in the tropics all the year round, which, in contrast to higher latitudes, favours year-long vitamin-D synthesis. We suggested that cholecalciferol administration to women from the menopause onwards and possibly also to elderly men, in an amount that raises plasma 25(OH)D levels to those of Curaçao women, may delay the occurrence of osteoporotic lesions. In the present study we investigated whether cholecalciferol administration to premenopausal and postmenopausal Dutch women would raise late winter/early spring plasma 25(OH)D levels to baseline 25(OH)D levels seen in Curaçao.

SUBJECTS AND METHODS

Subjects

A total of 105 women were enrolled in the study. They were ambulatory and had no major ailments. They comprised: (1) forty-one (twenty black, twenty-one white) postmenopausal Curaçao women, aged 64–89 years, mean 75·3 (SD 5·8) years; (2) fifty-eight postmenopausal white Dutch women, aged 54–65 years, mean 61·2 (SD 2·4) years, and (3) six apparently healthy premenopausal white Dutch women, aged 23–40 years, mean 30·1 (SD 6·9) years. Five of the premenopausal women took oral contraceptives.

None of the women used drugs known to alter vitamin-D or bone metabolism (e.g. anticonvulsants, corticosteroids and postmenopausal oestrogens). Informed consent was obtained from all subjects. The study was in agreement with local ethical standards and the Helsinki declaration of 1975, as revised in 1989.

Study design

The women having supplementary cholecalciferol received 10 or 20 μg oral cholecalciferol (Duphar bv, The Netherlands)/d. Twenty postmenopausal Dutch women were given a placebo. The women were randomly assigned to receive placebo, 10 or 20 μg cholecalciferol/d.

Postmenopausal black (n *20*) *and white* (n *21*) *Curaçao women.* Supplementary cholecalciferol was given for 9 weeks (from October to December 1992). Ten black and ten white women received 20 μg/d as a single dose. Ten black and eleven white women received an equal daily amount, administered as two doses of 10 μg during the day. Plasma 25(OH)D, $1,25(OH)_2D$ and parathyroid hormone (PTH), serum Ca and phosphate, and urinary Ca, phosphate and creatinine concentrations were determined before and after 1, 5 and 9 weeks supplementation.

Postmenopausal white Dutch women (n *58*). Cholecalciferol was administered for 5 weeks in late winter/early spring (from 6 April to 13 May 1993). The women received daily doses of 20 μg cholecalciferol (*n* 19), 10 μg cholecalciferol (*n* 19), or 135 mg cellulose (placebo; *n* 20). To avoid detection of dissimilarity between supplements, cholecalciferol was administered in cellulose-filled capsules that resembled the placebo. Plasma 25(OH)D, $1,25(OH)_2D$ and PTH, and serum Ca and phosphate concentrations of all women were determined before and after 5 weeks supplementation.

Premenopausal white Dutch women (n *6*). Cholecalciferol was administered for 4 weeks in late winter (from 4 March to 1 April 1992). The women received 20 μg cholecalciferol daily. Plasma 25(OH)D, $1,25(OH)_2D$ and PTH were determined before and after 4 weeks. Serum Ca and phosphate were measured weekly.

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Sampling, sample processing and analytical methods

Blood and EDTA-anticoagulated blood were collected by venepuncture for the preparation of serum and plasma respectively. Samples of urine were collected after morning voidance and after a subsequent 2 h fast. These were either analysed immediately or stored at −20° until analysed. Serum and urinary Ca and phosphate concentrations of the Curaçao women were determined in the local Public Health Laboratory. Plasma, serum and urine remainders were transported to The Netherlands in solid CO_2 for further analysis in the University Hospital Groningen.

Serum and urinary Ca (ortho cresolphthalein complexone method) and phosphate (molybdate method), and urinary creatinine (picric acid method) were measured with a Kodak Ektachem 500 (Eastman Kodak Company, Rochester, NY, USA) in The Netherlands and a Beckman Astra-8 autoanalyser (Beckman, Fullerton, CA, USA) in Curaçao. Reference ranges for serum Ca and phosphate were: 2·25–2·75 and 0·74–1·52 mmol/l (The Netherlands), and 2·20–2·60 and 0·70–1·60 mmol/l (Curaçao) respectively. Between-series coefficients of variation (CV) for serum Ca and phosphate concentrations in the reference ranges amounted to: 1·2 and 1·5% (The Netherlands) and 1·5 and 2·0% (Curaçao) respectively. Intact PTH (PTH amino acids 1–84) was measured with a two-site immunoradiometric assay (IRMA) by using the commercial kit of the Incstar Corporation (Stillwater, MN, USA). The between-series CV for quality-control samples at 3·4, 20·0 and 32·5 pmol/l were 9·2, 9·2 and 9·6% respectively. $25(OH)D_2$ and $25(OH)D_3$ were measured as 25(OH)D, by using solid-phase prepurification followed by a competitive radio-binding assay with tritium-labelled $25(OH)D_3$ and vitamin D-binding protein from human serum. Between-series CV at 16, 62 and 101 nmol/l were 13, 12 and 13% respectively. $1,25(OH)_2D_2$ and $1,25(OH)_2D_3$ were determined as $1,25(OH)_2D$ with the kit of the Incstar Corporation, based on solid-phase prepurification followed by a competitive radioreceptor assay with tritium-labelled $1,25(OH)_2D_3$ and a thymus receptor. The between-series CV at 25, 93, and 138 pmol/l were 21, 16, and 14% respectively.

Statistical analyses

Independent t tests were used for establishing between-group differences before supplementation (Table 1). Values of $P < 0{\cdot}05$ were considered significant. Longitudinal results from the Curaçao study were analysed by repeated measurement (ANOVA; Stevens, 1986). Values that showed supplementation effects were subsequently investigated by the modified Tukey post-hoc procedure for one-sample repeated measurements at $P < 0{\cdot}05$. After verification of parallel line assumption, coincidences of analyte courses of different Curaçao groups (black *v.* white; 2×10 *v.* 20 μg) were tested with repeated measurement analysis. Dependent t tests were used for longitudinal data from the two Dutch studies. Values of $P < 0{\cdot}05$ were considered significant. For between-group comparison of data obtained from two sampling points during the study, analyses of covariance (ANCOVA) were used, with time as covariate. An example is the analysis of differences in 25(OH)D courses of postmenopausal Curaçao and Dutch women from baseline to 4–5 weeks supplementation.

RESULTS

Baseline values

Baseline values for plasma 25(OH)D, $1,25(OH)_2D$ and PTH of women in all groups are given in Table 1. The black and white postmenopausal Curaçao women taking part in the study did not differ in age, or in plasma 25(OH)D, $1,25(OH)_2D$ and PTH concentrations.

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Table 1. *Plasma 25-hydroxycholecalciferol (25(OH)D), 1,25-dihydroxycholecalciferol ($1,25(OH)_2D$) and parathyroid hormone (PTH) concentrations in postmenopausal black and white Curaçao women, and postmenopausal and premenopausal white Dutch women in late winter*

(Mean values and standard deviations)

		Age (years)		25(OH)D (nmol/l)		$1,25(OH)_2D$ (pmol/l)		PTH (pmol/l)	
	n	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Post Cur, black	20	73·8	4·0	88·3	28·2	98·0	53·5	2·3	1·3
Post Cur, white	21	75·4	7·1	82·0	25·8	78·6	46·3	1·9	1·1
Post Cur, all	41	75·3	5·8	85·1	26·9	88·3	50·4	2·1	1·2
Post Neth	58	61·2***†	2·4	58·5***†	23·8	91·7	32·1	3·9***†	1·3
Pre Neth	6	30·1***	6·9	46·2***	13·3	81·9	29·6	1·9	1·4

Post, postmenopausal; Pre, premenopausal; Cur, Curaçao; Neth, The Netherlands; Post Cur all, pooled data from black and white postmenopausal women in Curaçao.

*** Mean values were significantly different from pooled value for black and white postmenopausal women in Curaçao ($P < 0·001$).

† Mean values were significantly different from those for premenopausal women in The Netherlands ($P < 0·02$).

For comparison with values for premenopausal and postmenopausal Dutch women the Curaçao women were, therefore, considered as a single group.

Plasma 25(OH)D concentration of the elderly Curaçao women was higher than that of the young and elderly Dutch women and plasma 25(OH)D concentration of the elderly Dutch women was higher than that of the young Dutch women.

There were no differences in plasma $1,25(OH)_2D$ between the groups. Plasma PTH of the elderly Dutch women was higher than that of the young Dutch women and of the elderly Curaçao women. Premenopausal Dutch women and the elderly Curaçao women did not differ in plasma PTH. Baseline serum Ca and phosphate of all women, and urinary Ca:creatinine, phosphate:creatinine and Ca:phosphate ratios of postmenopausal Curaçao women were within the reference ranges of our laboratory.

Effects of cholecalciferol and placebo

Fig. 1 shows the changes in plasma 25(OH)D, $1,25(OH)_2D$ and PTH following cholecalciferol supplementation of postmenopausal black and white Curaçao women (a), postmenopausal Dutch women (b) and premenopausal Dutch women (c). The changes in plasma 25(OH)D, $1,25(OH)_2D$ and PTH following placebo administration to postmenopausal Dutch women are given in Fig. 2.

Postmenopausal Curaçao women. There were no significant differences in baseline plasma 25(OH)D, $1,25(OH)_2D$ or PTH concentrations between black (*n* 20) and white (*n* 21) postmenopausal Curaçao women. Changes following cholecalciferol administration were also similar in the two groups, and similar also whether the vitamin was taken as 20 μg once daily or in two doses of 10 μg (results not shown). Black and white postmenopausal Curaçao women were therefore considered as a single group (Fig. 1(a)). The pooled data showed that supplementation caused statistically significant increases of 25(OH)D, $1,25(OH)_2D$ and PTH. Stable levels were reached within 1 week. Serum Ca and phosphate, and urinary Ca:creatinine, phosphate:creatinine and Ca:phosphate ratios did not change. Mean serum concentrations at baseline and after 9 weeks supplementation were: Ca

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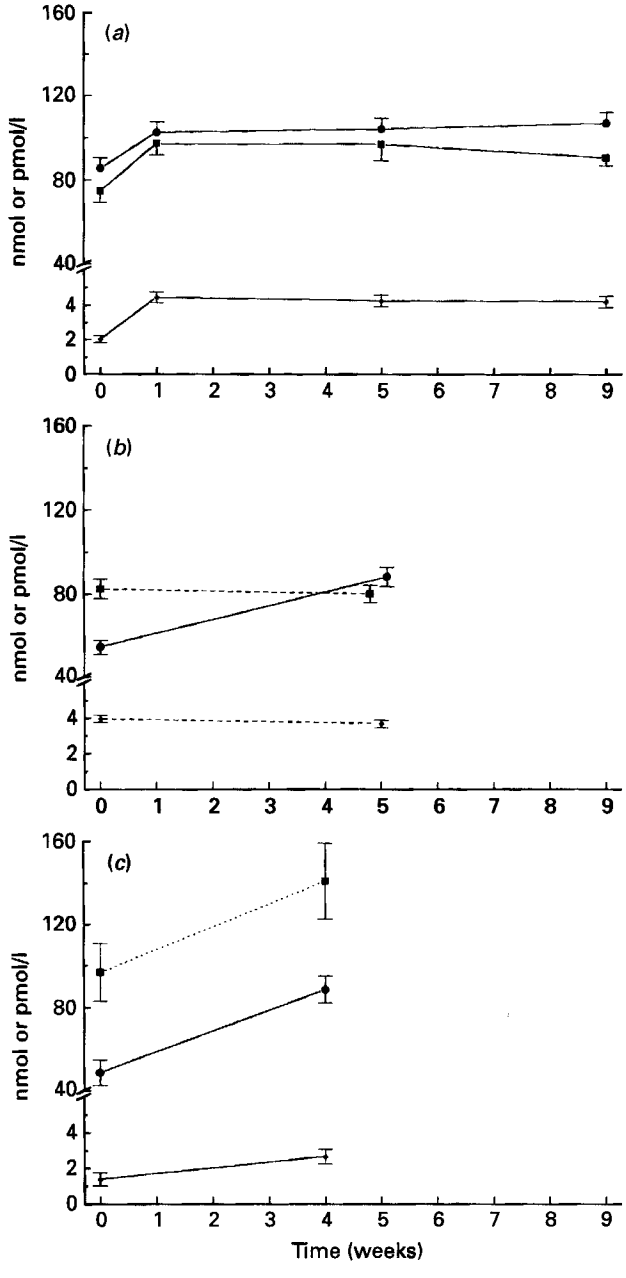

Fig. 1. Courses of plasma 25-hydroxycholecalciferol (25(OH)D; ●), 1,25-dihydroxycholecalciferol (1,25$(OH)_2$D; ■) and parathyroid hormone (PTH; ◆) concentration in (a) postmenopausal black (n 20) and white (n 21) Curaçao women, (b) postmenopausal white Dutch women (n 38) and (c) premenopausal white Dutch women (n 6) following cholecalciferol supplementation (10 or 20 μg/d). Values for 25(OH)D are nmol/l; those for 1,25$(OH)_2$D and PTH are pmol/l. For details of subjects and procedures see pp. 638–639. Values are means with their standard errors represented by vertical bars. Repeated measurements statistics and dependent t tests revealed time-dependent increases of 25(OH)D levels in all groups, of 1,25$(OH)_2$D in postmenopausal Curaçao women, and of PTH levels in postmenopausal Curaçao women and premenopausal Dutch women (uninterrupted lines).

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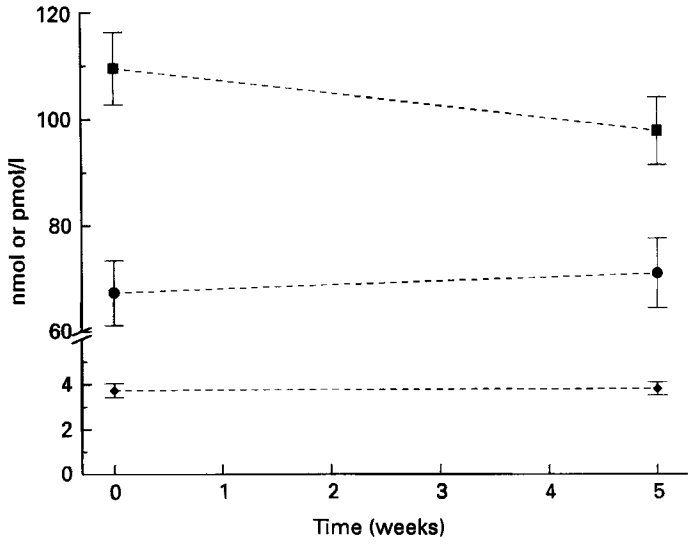

Fig. 2. Courses of plasma 25-hydroxycholecalciferol (25(OH)D; ●), 1,25-dihydroxycholecalciferol (1,25$(OH)_2$D; ■) and parathyroid hormone (PTH; ◆) concentration following administration of cellulose (placebo) to postmenopausal white Dutch women (*n* 20). For details of subjects and procedures see pp. 638–639. Values for 25(OH)D are nmol/l; those for 1,25$(OH)_2$D and PTH are pmol/l. Values are means with their standard errors represented by vertical bars. Repeated measurements statistics and dependent *t* tests revealed no changes.

2·30 (SD 0·20) and 2·47 (SD 0·11) mmol/l and phosphate 1·16 (SD 0·15) and 1·13 (SD 0·15) mmol/l respectively.

Postmenopausal Dutch women. Baseline values of 25(OH)D, 1,25$(OH)_2$D and PTH, and their changes during cholecalciferol supplementation were not different for postmenopausal Dutch women who received 10 (*n* 19) or 20 (*n* 19) μg/d (results not shown). The pooled data showed that 25(OH)D, but not 1,25$(OH)_2$D and PTH, increased (Fig. 1(b)). There were no significant changes in the twenty postmenopausal Dutch women receiving placebo (Fig. 2). Administration of cholecalciferol or placebo did not affect serum Ca and phosphate. Mean serum concentrations for vitamin-D-supplemented women at baseline and after 5 weeks were: Ca 2·47 (SD 0·20) and 2·44 (SD 0·15) mmol/l and phosphate 1·23 (SD 0·19) and 1·26 (SD 0·12) mmol/l respectively.

Premenopausal Dutch women. In premenopausal women receiving cholecalciferol the 25(OH)D and PTH levels rose markedly, whereas 1,25$(OH)_2$D levels did not change (Fig. 1(c)). Their serum Ca and phosphate concentrations did not change. Mean serum concentrations at baseline and after 4 weeks were: Ca 2·41 (SD 0·13) and 2·50 (SD 0·08) mmol/l and phosphate 1·07 (SD 0·07) and 1·13 (SD 0·12) mmol/l respectively.

Changes and endpoints in plasma 25(OH)D following cholecalciferol supplementation. Following 5 weeks supplementation with 10 or 20 μg cholecalciferol/d, postmenopausal Dutch women reached mean plasma 25(OH)D levels of 87·9 (SD 28·1) nmol/l (*n* 38). These levels were not significantly different from baseline levels of postmenopausal Curaçao women (mean 85·1 (SD 26·9) nmol/l; *n* 41; Table 1). They were, however, lower than 25(OH)D levels of postmenopausal Curaçao women after 5 weeks supplementation with 20 or 2 × 10 μg/d (mean 102·6 (SD 28·8) nmol/l; *n* 41). The changes in plasma 25(OH)D of postmenopausal and premenopausal Dutch women were similar (parallel, coincident), but both significantly different from those of postmenopausal Curaçao women (parallel, but not coincident).

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DISCUSSION

Plasma 25(OH)D concentration usually decreases with advancing age, a condition associated with development of secondary hyperparathyroidism and increasing osteoporosis risk (Khaw *et al.* 1992). Nevertheless, compared with their significantly younger Dutch counterparts the postmenopausal women in Curaçao had higher plasma 25(OH)D, lower PTH and similar $1,25(OH)_2D$ concentrations (Table 1). These findings are at variance with those of our previous study (Dubbelman *et al.* 1993) in which postmenopausal women in Curaçao had higher 25(OH)D, similar PTH and higher $1,25(OH)_2D$ concentrations. A possible explanation is that the present postmenopausal Dutch women (61·2 (SD 2·4) years) were considerably younger than their previously studied institutionalized Dutch counterparts (63–83 years). Compared with our previous findings from premenopausal Dutch women the present group of premenopausal Dutch women showed similar plasma 25(OH)D, $1,25(OH)_2D$, and PTH concentrations. Those of 25(OH)D and $1,25(OH)_2D$ were found to be lower, compared with Curaçao counterparts (Dubbelman *et al.* 1993). Following 4 weeks vitamin-D supplementation, premenopausal Dutch women exhibited still lower 25(OH)D, but somewhat higher $1,25(OH)_2D$ and PTH concentrations, compared with baseline values of premenopausal Curaçao women (Dubbelman *et al.* 1993).

Higher plasma 25(OH)D concentrations in Curaçao are caused by year-long, season-independent, abundant sunlight, which favours vitamin-D synthesis in skin. Curaçao is a tropical island located in the Caribbean sea at 12° north latitude. The island is predominantly inhabited by subjects of West-African origin. Most white women are of Dutch descent. Dietary habits are essentially Western, with a generally low intake of Ca because of low milk consumption.

We did not observe differences in baseline plasma 25(OH)D concentrations of black and white postmenopausal Curaçao women. This finding is in agreement with a study of Meier *et al.* (1991), who found similar 25(OH)D concentrations in premenopausal black and white women living in the New York City area. However, Bell *et al.* (1985) found lower 25(OH)D concentrations in young blacks living in South Carolina. In contrast to white subjects, black subjects did not show a rise in serum vitamin D and 25(OH)D, following a single exposure to a relatively small ultraviolet radiation dose (Clemens *et al.* 1982). The observation is explained by lower previtamin D_3 synthesis rate in pigmented skin (Holick *et al.* 1981).

The present study shows that placebo-controlled (postmenopausal Dutch women) and placebo-uncontrolled (postmenopausal Curaçao women and premenopausal Dutch women) administration of 10 or 20 μg cholecalciferol/d for 4–5 weeks during late winter/early spring raised the concentration of 25(OH)D in the plasma of premenopausal and postmenopausal women living in a northern latitude (The Netherlands) to those of postmenopausal women living in the tropics (Curaçao). The similarity in response to supplementation with 10 μg/d and 20 μg/d suggests that the lower dose is adequate. It is conceivable that a smaller dose might have the same effect. The treatment had no effect on serum Ca and phosphate concentrations (all women), or on urinary Ca and phosphate excretion (Curaçao), which implies that no short-term toxic effects are likely to occur.

Vitamin-D toxicity has been reported when young children were given 45 μg or more daily, but young children are especially sensitive to vitamin-D toxicity (National Research Council, 1989). A high concentration of 25(OH)D in plasma may play a role in this. The highest 25(OH)D level in the present study was 188 nmol/l. Hypercalcaemia and hyperphosphataemia due to vitamin-D intoxication are usually accompanied by plasma 25(OH)D levels above 375 nmol/l (Holick, 1994).

Absolute increases of plasma 25(OH)D following 4–5 weeks cholecalciferol sup-

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plementation were similar in premenopausal and postmenopausal Dutch and postmenopausal Curaçao women. Taking all data together, the median 25(OH)D increase amounted to 24 nmol/l. Our results indicate that in the 10, 20 and 2×20 μg dose range the absolute 25(OH)D increase tended to some degree to be independent of baseline plasma 25(OH)D, daily dose or frequency of administration of a given dose.

Similar effects of 10 and 20 μg have been reported previously (Lips *et al.* 1988), and seem to argue against the notion that conversion of cholecalciferol to 25(OH)D is loosely regulated (Norman, 1990; Holick, 1994). Considering the similarity in 25(OH)D responses following a single 20 or a 2×10 μg daily dose, it is hardly conceivable that in this dose range gastrointestinal fractional cholecalciferol absorption decreases with increasing cholecalciferol dose.

A possible explanation for the similarity in plasma 25(OH)D responses following 10 and 20 μg cholecalciferol/d is that, like vitamin E and carotenoids (Traber & Kayden, 1987; Kaplan *et al.* 1990), adipose tissue and other organs function as vitamin-D-buffering systems. Humans have the capacity to store circulating cholecalciferol, notably in adipose tissue and muscle (Mawer *et al.* 1972). Cholecalciferol taken orally probably leads to a different body distribution from that resulting from synthesis in skin. Cholecalciferol is believed to be removed from skin by binding to the vitamin-D-binding protein (Holick *et al.* 1981), whereas orally administered cholecalciferol enters the body via chylomicrons (Holick, 1994).

At present the effects of cholecalciferol are best described as maintenance of extracellular Ca and phosphate in a supersaturated state which results in bone mineralization (Holick, 1994). This thesis is supported by studies that showed beneficial effects of cholecalciferol supplementation in prevention or postponement of postmenopausal osteoporosis (Dawson-Hughes *et al.* 1991; Chapuy *et al.* 1992) and our observation that, in contrast to white women living in northern latitudes, postmenopausal white Curaçao women do not show signs of compression fractures of their lumbar vertebrae (Dubbelman *et al.* 1993). The young Dutch women had baseline PTH levels similar to those of the elderly Curaçao women, whereas those of the elderly Dutch women were higher (Table 1). Since high PTH levels are usually associated with bone Ca resorption, it is likely that premenopausal Dutch women (because of the protective influence of oestrogens on bone resorption) and postmenopausal Curaçao women (because of their better vitamin-D status) were in, or close to, bone Ca balance, whereas postmenopausal Dutch women (because of their lower vitamin-D status and lack of oestrogen protection) were in negative bone Ca balance.

Lips *et al.* (1988) reported 15% decreases of plasma PTH after 3 months cholecalciferol supplementation of two groups of elderly Dutch women (81 (SD 9) and 84 (SD 6) years) with very low baseline 25(OH)D levels (23·6 (SD 8·9) and 23·8 (SD 13·3) nmol/l respectively). Their results and those of others (Dawson-Hughes *et al.* 1991; Chapuy *et al.* 1992) suggested that secondary hyperparathyroidism-induced bone Ca resorption diminished. We did not observe plasma PTH changes in postmenopausal Dutch women (mean 61 (SD 2) years) after 5 weeks cholecalciferol supplementation (Fig. 1(b)). Decrease of PTH may take longer than 5 weeks. Quite unexpectedly, cholecalciferol supplementation caused PTH to increase in premenopausal Dutch women (mean 30 (SD 7) years; Fig. 1(c)), and both PTH and $1,25(OH)_2D$ to increase in postmenopausal Curaçao women (mean 75 (SD 6) years; Fig. 1(a)). The increase in plasma $1,25(OH)_2D$ of premenopausal Dutch women did not reach statistical significance, probably because of the small number of subjects investigated. Because of oestrogen protection (premenopausal Dutch women) and high baseline vitamin D status (postmenopausal Curaçao women), we speculate that we are dealing with a natural reaction in women who are probably in bone Ca balance. Similar responses of PTH and $1,25(OH)_2D$ were observed following administration of oestrogens to postmenopausal

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women. Stock *et al.* (1985) found that PTH (amino acids 44–68) concentration decreased after 2 weeks and subsequently increased after 8 weeks, whereas 1,25(OH)$_2$D concentration was higher from 2 weeks.

In conclusion, this study shows that 4–5 weeks oral administration of 10 and 20 μg cholecalciferol/d to premenopausal and postmenopausal white women in late winter/early spring causes plasma 25(OH)D to reach baseline levels characteristic of postmenopausal women living in the tropics. A daily dose of 10 μg appears to be sufficient. The good condition of the lumbar vertebrae of postmenopausal white Curaçao women suggests that prevention of the decline in the plasma 25(OH)D in winter reduces bone demineralization of postmenopausal women living in northern latitudes (Jonxis, 1994).

Note by Professor J. H. P. Jonxis added during editing

The Committee on Nutrition of the Elderly of The Food and Nutrition Council of the Netherlands has recommended that men and women aged 65–75 years who are exposed to sunlight during the summer months should take a supplement of 2·5 μg vitamin D/d. Those aged 65–75 years who are rarely exposed to sunlight, and all men and women aged over 75 years, should take a daily supplement of 7·5–10 μg.

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