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Seasonal variation in vitamin D

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FROM VITAMIN D TO STEROID HORMONE OF SUNLIGHT

Privational rickets was a scourge of industrial cities in the 19th and early 20th centuries. Recognition of the antirachitic effect of meat fat in the 1920s, as well as the protective effects of sunlight and u.v. radiation, led to the discovery of vitamin D. As a result of effective public health measures privational rickets virtually disappeared from the UK by 1940. In the USA where milk is routinely fortified, vitamin D deficiency now occurs only in unusual circumstances, but childhood rickets and osteomalacia in adults reappeared in the UK in the 1960s among immigrant Asian communities (Clements, 1989; Henderson *et al.* 1990).

Vitamin D is provided from both endogenous sources (synthesized in the skin from 7-dehydrocholesterol (7-DHC) in a reaction catalysed by u.v. light) and from the diet. It is transported in the blood bound to vitamin D-binding protein (DBP) and activated by hydroxylation in the liver (to yield 25-hydroxycholecalciferol (25-OH D)). Since this step is not tightly regulated, circulating 25-OH D concentrations are considered the best indicator of vitamin D stores. The second site of active metabolism occurs in the kidney where a classic mixed-function cytochrome P-450 steroid hydroxylase (*EC* 1.14.15.6) yields the principal active metabolite 1α,25-dihydroxycholecalciferol (1α,25-$(OH)_2$ D). Conversion to the active hormone is under strict control regulated by the stimulatory effect of parathyroid hormone (PTH) on renal 1α-hydroxylase (*EC* 1.14.15.3) activity, and feedback inhibitory control by 1,25-$(OH)_2$ D (Reichel *et al.* 1989).

The mechanism of action of 1,25-$(OH)_2$ D is similar to that of other steroid hormones, interacting with an intracellular receptor protein (vitamin D receptor, which has sequence homology with other steroid-hormone receptors). The steroid–receptor complex is then localized to the nucleus of target cells to initiate the synthesis (or repression) of specific proteins responsible for a spectrum of biological responses. While the important role of 1,25-$(OH)_2$ D on intestine, bone, kidneys and parathyroid glands in the maintenance of Ca metabolism and mineral homeostasis has long been recognized, it is now known that vitamin D receptors occur in many tissues not primarily related to mineral homeostasis. Evidence from animal studies has suggested that 1,25-$(OH)_2$ D may have a wider biological role, as it influences cellular proliferation and differentiation of several tissues and also plays a part in immunoregulation (Reichel *et al.* 1989; Yang *et al.* 1993).

SEASONALITY OF VITAMIN D

Clinical observations in the past indicated that rickets was common in spring but rare in autumn, suggesting that summer sunshine was an important source of vitamin D. Using bioassay techniques, seasonal variation in plasma antirachitic activity was detected in southern latitudes of the USA, but effects of sunshine were thought to be minimal in the

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UK. The development of biochemical assays for vitamin D metabolites permitted an examination of the relative importance of diet and endogenous skin synthesis (Haddad & Hahn, 1973) and led to the finding of a seasonal variation in plasma 25-OH D levels in healthy white subjects in cross-sectional and longitudinal studies in Britain (McLaughlin *et al.* 1974; Stamp & Round, 1974). This was the first demonstration of prominent seasonal variation in an important plasma constituent. Peak 25-OH D levels were found in the autumn and were unrelated to dietary vitamin D intake. This indicated that, contrary to earlier views, summer sunshine was an important determinant of vitamin D nutrition in Britain. The finding of low dietary intakes in some healthy subjects, together with the fact that vitamin D intake did not correlate with peak autumn plasma levels, suggested that summer sunshine might indeed make a greater contribution than diet to vitamin D stores.

Subsequent studies from many parts of the world have confirmed a significant seasonal variation of 25-OH D in all groups examined, and sunlight exposure is now accepted as the major determinant of vitamin D stores (Haddad & Hahn, 1973; Fraser, 1983). Studies of selected groups have provided additional information on the factors affecting seasonal variation in vitamin D levels, and insights into causes of clinical vitamin D deficiency.

Age and sex

In a cross-sectional study of a selected healthy population in Baltimore aged from 20 to 94 years, significant seasonal fluctuation occurred in both men and women, and was unaffected by age. In the combined population the values for 25-OH D increased from a nadir in April–May of 72·9 nmol/l to a zenith in October of 95·8 nmol/l. The mean amplitude of the cyclic sine wave was similar in men and women (11·9 (SD 3·02) *v.* 11·0 (SD 3·48) nmol/l). Since control of the circulating active hormonal form of vitamin D is tightly regulated, it was interesting that there was also a significant seasonal variation in 1,25-$(OH)_2$ D for both sexes, suggesting a substrate–product relationship (Sherman *et al.* 1990).

An inverse seasonal relationship has been reported between seasonal serum 25-OH D and PTH concentrations. In a large cross-sectional study of healthy white postmenopausal American women in Massachusetts who had low median Ca (408 mg/d) and vitamin D (2·8 μg/d) intakes, highest PTH concentrations were found in the spring, when 25-OH D levels were lowest (Krall *et al.* 1989). Elderly patients in Boston also showed a significant inverse correlation between PTH and serum 25-OH D. Of the volunteers with elevated PTH, 73% had 25-OH D values under 37·5 mmol/l (Webb *et al.* 1990). Postmenopausal white women (aged 52–77 years) from the mid-west of the USA found to have decreased serum 25-OH D had low vertebral bone density compared with matched controls with normal circulating 25-OH D. Significant seasonal variation in serum 25-OH D was observed in the controls but not in the low-25-OH D group. Since the women had similar dietary vitamin D intakes, the results indicated that in white postmenopausal women, vitamin D deficiency is primarily accounted for by diminished sunlight exposure (Villareal *et al.* 1991). However, serum total and ionized Ca levels, which are under tight homeostatic control, do not show seasonal changes and are relatively stable with age (Sherman *et al.* 1990).

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Ageing and immobility

The lowest serum 25-OH D concentrations have been found in institutionalized elderly people in countries (such as Britain) that do not routinely fortify foods with vitamin D. Three elderly populations in Boston, grouped according to disability, were investigated to assess the relative seasonal contributions of diet and outdoor activity as sources of vitamin D. They comprised free-living elderly subjects (mean age 80 (SD 6) years); independently mobile people in a residential home (mean age 81 (SD 8) years); and limited mobility nursing home residents (mean age 82 (SD 9) years). Sunshine u.v.-B exposure measured by polysulphone badges showed marked differences between groups in their solar u.v.-B exposure. This was greatest in free-living elderly, but even the most care-dependent residents gained some outdoor exposure in midsummer (Webb *et al.* 1990).

Serum 25-OH D concentrations and seasonal changes in healthy mobile independent elderly are similar to those in young adults. However, seasonal changes decline in magnitude in elderly subjects with decreasing mobility, resulting in reduced outdoor activity and sunshine exposure. This is accompanied by a decrease in the seasonal variation related to decreased u.v. exposure. Dependent institutionalized elderly individuals have much lower circulating concentrations of 25-OH D at all times of the year, and are much more likely to have low levels associated with privational disease during both winter and summer months (Sherman *et al.* 1990; Webb *et al.* 1990).

Dietary and supplemental vitamin D

The diet is thought to contribute very little to vitamin D stores, and dietary intake of vitamin D fails to provide an adequate amount for institutionalized elderly with minimal outdoor activity, even in the USA where milk is fortified. However, vitamin supplements can modulate the normal seasonal variation in serum 25-OH D, and use of a vitamin D supplement providing 10 μg (400 IU) vitamin D maintained serum 25-OH D concentrations at satisfactory levels in institutionalized elderly in Boston throughout the year. In contrast, fit independent elderly, who enjoy the increased sunlight exposure their increased mobility brings, had seasonal serum 25-OH D levels comparable with those achieved by institutionalized elderly taking vitamin D supplements. Seasonal change in vitamin D status was apparent in nursing home residents as a whole, but was small compared with differences between elderly with and without vitamin D supplements. Seasonal variation was smaller in those who took a daily multivitamin tablet. In the healthy free-living elderly, dietary intake of vitamin D is less important (Webb *et al.* 1990).

The modulation of seasonal changes by vitamin supplements has also been shown in healthy white postmenopausal American women (mean age 58 (range 43–71) years). In this group the overall inverse relationship between serum 25-OH D and PTH levels was found to be dependent on vitamin D intake. In women whose estimated intake of vitamin D was under 5·5 μg/d the mean PTH levels were lowest between August and October, when peak values for 25-OH D were obtained, and highest between March and May, when 25-OH D trough levels were observed. However, for those women with vitamin D intakes of more than 5·5 μg/d, serum PTH and 25-OH D levels did not vary with the season. Seasonal and reciprocal changes in PTH were no longer apparent at 25-OH D levels >95 nmol/l, which is well above what is considered 'normal' (Krall *et al.* 1989).

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Skin pigmentation and vegetarian diet

As a result of immigration, about 2·5% of United Kingdom residents are now of south Asian or Indian subcontinent origin. Clinically significant vitamin D deficiency was first recognized among Glasgow's immigrant Asian community in the 1960s and is now known to be endemic in the British Asian population (Clements, 1989; Henderson *et al.* 1990). Latitude and sunshine exposure have been considered important determinants of Asian rickets in the UK, but even in the south of Britain subclinical vitamin D deficiency is prevalent among apparently healthy non-hospitalized Asians, and bone biopsy has shown that a high proportion of Asian outpatients attending medical clinics have histological osteomalacia (Finch *et al.* 1992*b*). Although some have implicated dietary factors in the aetiology, others have considered inadequate exposure to naturally occurring u.v. light to be an important factor. The British Asian population constitute the largest reservoir of endemic vitamin D deficiency in the UK but darker skinned people in Britain originating from Africa or the West Indies do not appear to be at risk of vitamin D deficiency.

Studies of seasonal changes in serum 25-OH D have provided useful insights in explaining the paradox of vitamin D deficiency among Asian immigrants. If inadequate solar exposure is to be considered an aetiological factor in vitamin D deficiency in Asian immigrants, there should be evidence of reduced seasonal variation in 25-OH D among vitamin D-deficient Asians. In Asians living in Rochdale a significant seasonal rise in serum 25-OH D was confirmed (Stephens *et al.* 1982). The seasonal increase in adult males was greater than that in adult females, and it was found that the vitamin D-replete subgroup (spring 25-OH D >12·5 nmol/l) achieved a mean autumn level (39·0 (SD 19·0) nmol/l) which was higher than in the vitamin D-deficient individuals (16·5 (SD 8·5) nmol/l). A highly significant relationship was observed between the seasonal change in serum 25-OH D concentrations and the prevailing (mean of spring and autumn) level. These results indicated that vitamin D-deficient Asians, who had an attenuated seasonal rise, responded to summer sunshine in a different way to vitamin D-replete Asians. The authors suggested that the most likely explanation for these findings was that vitamin D-deficient Asians were exposed to less summer sunshine, despite the fact that their assessment of mean solar exposure showed no significant difference between the groups (Stephens *et al.* 1982).

Asian immigrants in Britain are heterogeneous but the Rochdale study did not distinguish between ethnic subgroups. A more recent report has suggested that an attenuated seasonal rise in vitamin D in some Asians may be due to culturally determined differences in diet (Fig. 1). In a large cross-sectional study in south London serum 25-OH D levels were measured in 297 adult Asian and sixty-eight white subjects. Seasonal variation was compared between subjects grouped according to ethnic origin, religion and dietary habit. A subgroup of Asians with symptoms and biochemical changes suggestive of osteomalacia underwent bone biopsy. Histological osteomalacia was detected in fifteen subjects (and borderline changes in a further thirteen subjects). The majority of these cases were among vegetarian Hindus. Significant seasonal variation was observed among all groups, but with lower peak and trough levels among Asians compared with white subjects. However, examining subgroups of Asians it was found that non-vegetarian Asians had similar seasonal rise and peak values to those of white subjects, while vegetarian Asians (who were overwhelmingly Hindus) had

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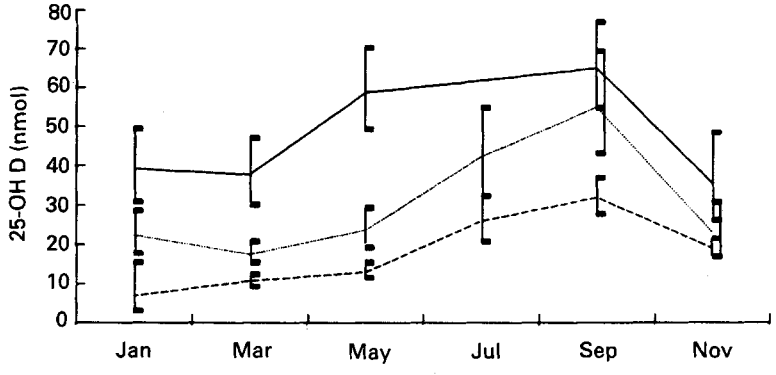

Fig. 1. Seasonal changes in serum 25-hydroxycholecalciferol (25-OH D) for white subjects (——), non-vegetarian Asians (·····) and vegetarian Asians (– – – –). Values are means with their standard errors represented by vertical bars. From Finch *et al.* (1992*a*). Reproduced by permission of editor of *European Journal of Nutrition*.

significantly lower peak values and an attenuated rise compared with white subjects and non-vegetarian Asians (Finch *et al.* 1992*a*).

These findings are paradoxical since *in vitro* studies have shown that the activity of hepatic 25-hydroxylase is greatest at low levels of vitamin D supply, and in white subjects the 25-OH D response to vitamin D administration is inversely related to the initial 25-OH D level. However, the findings in south London Asians are consistent with the earlier observation in Rochdale that vitamin D-deficient Asians responded to summer sunshine with an attenuated rise in 25-OH D, compared with vitamin D-replete Asians. Analysis of the findings on seasonal changes in 25-OH D in Asians resident in the south of England by religious and cultural groups indicate that Asians have the potential for achieving the same peak 25-OH D levels as the indigenous white population. However, in lactovegetarians (largely Hindus) seasonal responses are blunted, resulting in significantly lower peak values than for white subjects or non-vegetarian Asians. Furthermore, vegetarian Asians who show this attenuated seasonal variation in vitamin D levels have a substantially greater risk of osteomalacia than non-vegetarian Asians.

Whether the effect of vegetarianism is due to accelerated catabolism of endogenous 25-OH D as a result of hyperparathyroidism consequent on a low-Ca, high-cereal diet (Clements, 1989), or other factors (such as impaired hepatic hydroxylation) remains obscure. In the south London study multivariate analysis failed to show an effect of vegetarian diet on PTH independent of osteomalacia (Finch *et al.* 1992*a*).

PHOTOBIOLOGY OF VITAMIN D

The recognition of seasonal variations in 25-OH D related to changes in sunlight has stimulated interest in the photobiology of vitamin D. When human skin is exposed to u.v.-B radiation (290–320 nm), high-energy u.v. photons enter the epidermis and cause photochemical transformations of 7-dehydrocholesterol (7-DHC) to previtamin D. Once formed, previtamin D undergoes temperature-dependent isomerization to vitamin D

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(cholecalciferol) which at body temperature takes about 2–3 d to reach completion. Vitamin D is then transported in the blood bound to DBP (Holick *et al.* 1981).

Endogenous synthesis of cholecalciferol from 7-DHC is related to the amount of biologically effective u.v. radiation, the duration of exposure of u.v. radiation, and to the degree of skin pigmentation. Recent research on how sunlight and diet bring about their effects on vitamin D metabolism suggest a complexity previously unthought of and partially explains how risk factors operate.

In experimental studies the formation of previtamin D in hypopigmented skin reaches a plateau after a short initial exposure to u.v. radiation. If exposure is prolonged the previtamin D, itself labile to sunlight, is converted to the biologically inert photoproducts lumisterol and tachysterol. Similarly, vitamin D formed from previtamin D by thermal isomerization over 2–3 d in the skin is also rapidly degraded by sunlight. Because DBP has little affinity to lumisterol or tachysterol, translocation of these photoisomers into the circulation is negligible and they are probably sloughed off in natural turnover of skin. Thus, photochemical conversion of previtamin D to lumisterol appears to limit previtamin D formation during excessive exposure to the sun, and prevents vitamin D intoxication after prolonged exposure to the sun (Holick *et al.* 1981).

As the melanin pigment concentrations in skin increase, time of exposure necessary to maximize previtamin D formation, but not content, increases from 30 min to between 1 and 3 h (depending on degree of skin pigmentation). However, regardless of skin type, previtamin D reaches a maximum and a plateau at about 15% of original 7-DHC concentration (Holick *et al.* 1981; Lo *et al.* 1986). Although the cutaneous level of 7-DHC and the efficiency of its conversion both fall with age, these factors do not appear to constrain the production of hydroxylated derivatives of vitamin D in healthy elderly. Differences in seasonal vitamin D noted between institutionalized and healthy fully-ambulant elderly subjects are largely explained by marked differences in solar exposure between groups (Webb *et al.* 1990). Experimental studies have confirmed that clothing also affects the vitamin D response to u.v.-B radiation (Matsuoka *et al.* 1992).

The practical result of these complex effects of sunlight on vitamin D metabolism is that a short initial summer exposure can provide the body with enough vitamin D for the next few days, irrespective of further exposure. Thus, although there is an important relationship between sunlight and circulating concentrations of 25-OH D, measurement of summertime hours of sunlight exposure cannot be expected to bear a simple relationship to the amount of vitamin D produced.

The amount of u.v.-B light incident on the earth's surface depends on the amount of ozone in the stratosphere and varies with season and latitude. Winter sunlight in high latitudes is ineffective for production of vitamin D, since when the sun is low in the sky its zenith angle increases and u.v.-B radiation is subject to more scattering and absorption by ozone than when the sun is directly overhead.

The zenith angle also increases with latitude. Thus, moving from the equator to Boston (42° N) increased the exposure time necessary to maximize previtamin D formation. In Boston, skin exposure to such sunlight as exists will not result in any synthesis of vitamin D between about 1 November and 1 March. Further north in Edmonton (10° N of Boston), synthesis of previtamin D ceases in October and does not begin until April. However, equivalent exposure times result in significant conversion of 7-DHC to previtamin D even in January at lower latitudes such as Los Angeles and Puerto Rico (Webb *et al.* 1988).

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POSSIBLE BIOLOGICAL AND CLINICAL SIGNIFICANCE OF SEASONAL VARIATION IN VITAMIN D

Are there any biological or clinical consequences for seasonal changes in vitamin D? First, the possible effects of seasonal vitamin D changes on mineral metabolism will be examined, and next, possible consequences for wider cellular functions of vitamin D. Of particular interest are biological phenomena or clinical conditions which have a seasonal or latitude gradient.

1,25-dihydroxycholecalciferol and calcium absorption

Serum Ca is tightly controlled, but a number of studies have reported that urinary Ca excretion appears to peak in summer months. This could be explained by higher intestinal Ca absorption in summer compared with winter, which was first reported in early balance studies (McCance & Widdowson, 1943; Malm, 1958). Recently, seasonal changes in Ca absorption have been demonstrated with radioisotope methods for assessing Ca absorption and retention. Fractional Ca absorption was significantly higher in postmenopausal women evaluated in the months from August to October than that from March to May (Krall & Dawson-Hughes, 1991). Interestingly, an increased level of Ca retention was associated with a lower rate of bone loss from the radius. These changes in Ca absorption and excretion could be accounted for by the small seasonal changes in hormonal metabolite of vitamin D ($1,25\text{-}(OH)_2$ D) found in some, but not all studies (Sherman *et al.* 1990).

Parathyroid hormone and bone mineral density

As mentioned previously, serum PTH levels have been found to have a significant inverse relationship with 25-OH D in postmenopausal women and elderly subjects. These findings have suggested that a seasonal increase in PTH levels results from a seasonal decrease in $1,25\text{-}(OH)_2$ D-stimulated intestinal absorption of Ca. The seasonal increase in PTH may have adverse effects on bone. It is well recognized that accelerated bone loss occurs in hyperparathyroidism, but it is not known whether slight increases in PTH also affect bone loss. However, seasonal variations in bone mineral content of metacarpal and lumbar spine bone have been reported in healthy postmenopausal women (Krolner, 1983). Postmenopausal women with low 25-OH D concentrations (and absent seasonal variation) were found to have significantly reduced vertebral bone density compared with controls. Increased PTH activity was the major determinant of the vertebral osteoporosis (Villareal *et al.* 1991). Serum concentrations of 25-OH D of >95 nmol/l, which are considerably above the lower end of the normal range, prevent a seasonal increase in PTH (Krall *et al.* 1989). Should we aim to maintain serum 25-OH D at a level sufficiently high to prevent fluctuation in PTH? Although even small increases in PTH may have a potentially harmful effect on the skeleton by accelerating bone loss in winter, such an effect, and its prevention by an increased intake of vitamin D, should be documented before specific recommendations are made.

Metabolic bone diseases

In the late 19th and early 20th century childhood rickets was known to have a peak seasonal incidence in late winter and early spring (Douglas, 1993). This is not surprising

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in view of the subsequent demonstration of seasonal changes in vitamin D. No such seasonal presentation has been described for adult osteomalacia but histological studies have shown that the major determinant of osteomalacia in Asian immigrants is a vegetarian diet. Vegetarian Asians have an abnormally attenuated seasonal rise in 25-OH D (Finch *et al.* 1992*a*). Increasing severity of osteomalacia is associated with increasingly strict vegetarian practice, which accounts for the excess risk of females, Hindus and Asians originating from East Africa (Finch *et al.* 1992*b*).

Seasonal changes in hip fractures, with a winter peak and summer nadir similar to seasonal vitamin D variation, have been recognized in both Britain and the USA. Analysis of data on 33 000 Scottish hospital admissions for fractured neck of the femur over a 5-year period (1983–87) showed significant seasonality, with seasonal amplitude about 10%, which becomes greater with age (Douglas, 1993). The role of vitamin D deficiency in the pathogenesis of osteoporotic fractures is controversial and any association may be coincidental. However, reports of seasonal changes in bone mineral density (Krolner, 1983), the recognition of inverse seasonal changes in PTH which may be responsible for accelerated bone loss (Krall *et al.* 1989; Webb *et al.* 1990), association of low 25-OH D levels with osteoporosis in postmenopausal women (Villareal *et al.* 1991), and the role of vitamin D in regulating the synthesis of the abundant bone-matrix protein osteocalcin (Reichel *et al.* 1989) make the possibility of a causal association with osteoporotic fractures plausible.

So much for the potential significance of seasonal variation on the classical role of vitamin D on bone mineral metabolism. Is there any evidence that seasonal variation might have consequences for the wider biological role of vitamin D on tissues not primarily related to mineral metabolism?

Behaviour

Specific vitamin D receptors are found in a number of parts of brain and spinal cord. From their anatomical distribution functional implications have been postulated. It has been suggested that seasonal changes in 25-OH D and 1,25-$(OH)_2$ D could underly seasonal changes in hormonal function, mood and behaviour, cell proliferation, differentiation and reproductive functions. Interestingly, vitamin D receptors have been detected in a number of brain sites in vertebrate seasonal breeding animals but were undetectable in the same tissues in non-seasonal breeders.

Biologists have proposed that all components of sunlight, u.v., visible and long-wave lengths, cooperate towards effective seasonal and diurnal adaptation to assure development, growth and reproduction for the survival of the species. These suggestions are speculative but it would be of interest to determine what changes in seasonal activity are attributable to visual light input via retinal and extraocular photoreceptors, and those which might be due to genomic target effects of vitamin D on brain vitamin D-receptor regions that parallel seasonal changes in u.v.-B-induced blood levels of the steroid hormone of sunlight (Stumpf & Privette, 1991).

The relevance to human behaviour, if any, is unknown. However, affective disorders with cyclic seasonal onset (SAD) also appear to have a striking latitude gradient. Mood changes are thought to be due to reduction in daylight hours and altered circadian secretion of melatonin. Whether seasonal changes in u.v. light and vitamin D contribute is not known.

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Cellular growth and proliferation

The notion that vitamin D may protect against colon cancer is based on epidemiological observations, animal experiments and intervention studies. Mortality rates are highest in areas of the USA and rest of the world that receive the least amounts of sunlight. Vitamin D metabolites suppress *in vitro* growth and increase differentiation of human colon cancer cells, and reduce incidence of experimental colon tumours in rats. In a prospective study moderate amounts of dietary vitamin D reduced the incidence of colon cancer in men in USA.

Additional evidence has come from a prospective study of about 26 000 volunteers which investigated the relationship between 25-OH D and risk of colon cancer in cases and controls. The risk of getting colon cancer was decreased threefold in people with a 25-OH D concentration of 20 ng/ml or more. The study did not take account of possible confounding factors such as consumption of milk, meat and fat in diet. However, these findings, in conjunction with previous epidemiological and laboratory studies, suggested that vitamin D metabolites, possibly working in conjunction with Ca, reduce colon cancer risk (Garland *et al.* 1989).

Immunoregulation

There is animal experimental evidence both *in vitro* and *in vivo* for an immunoregulatory role for 1,25-$(OH)_2$ D in both lymphocytes and monocytes (Yang *et al.* 1993), but the pathophysiological implications of these properties have yet to be established in a clinical context. However, some clinical observations are of interest. Privational rickets is associated with increased frequency of infections and impaired neutrophil phagocytosis (Reichel *et al.* 1989). A significant excess of tuberculosis (TB) in Hindu compared with Muslim Asians has been reported, and more recently a case–control study of Indian-subcontinent Asians in south London has shown a significant trend of increasing risk of TB with decreasing frequency of meat or fish consumption. Strict lactovegetarians (never eat meat or fish) had an 8·5-fold risk compared with those who took meat or fish daily. These results suggest that a vegetarian diet may be an independent risk factor for TB in immigrant Asians. Since vitamin D deficiency is more common among vegetarian Asians, who have an attenuated seasonal response, and it is known to have effects on immunological function in animals, vitamin D deficiency may be the factor in a vegetarian diet responsible for reduced immunocompetence and subsequent reactivation of TB.

A number of other incompletely understood disorders are known which have a prominent seasonal component and/or whose prevalence is affected by latitude; they include multiple sclerosis, where mortality rates show a clear north–south gradient, and ischaemic heart disease, where mortality rates are affected by both season and by latitude. Disorders of cellular proliferation and differentiation such as psoriasis, and various common malignancies (colon and prostate cancer) also show prevalence rates which vary with latitude.

CONCLUSION

Recognition of seasonal changes in vitamin D was an important observation in establishing the crucial role of u.v. radiation in the generation of 1,25-$(OH)_2$ D, the

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steroid hormone of sunlight. Various factors which affect seasonal variation in vitamin D are now understood, and there is growing understanding of the additional biological roles for this steroid hormone in many organs and tissues related to cellular growth and differentiation. However, much remains to be learned about the biological significance of these seasonal changes, especially for the wider cellular functions of vitamin D. The present review ends on a speculative note by suggesting that clinically dissimilar diseases may share an aberration in vitamin D. Nevertheless, the identification of a number of important clinical disorders characterized by seasonality or latitude prevalence provides a challenge to biologists and clinicians, and may suggest opportunities for epidemiological, clinical and laboratory investigation exploring the clinical relevance of seasonality.

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