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Seasonal variation of 1,25-dihydroxyvitamin D and its association with body mass index and age

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ABSTRACT

Under most normal conditions the serum level of 1,25-dihydroxyvitamin D is constant throughout the year, due to tight biochemical regulation. In contrast to this, the level of 25-hydroxyvitamin D is variable through the year, being largest in late summer, due to photosynthesis in the skin. The vitamin D status is usually assessed by measuring the level of the latter vitamin D derivative, rather than that of the presumably most active derivative $1,25(OH)_2$ vitamin D.

We here show that for persons with a high body mass index (BMI) there is a significant seasonal variation, not only of 25(OH) vitamin D, but also of $1,25(OH)_2$ vitamin D. The variation seems to be largest for those with the poorest vitamin D status. Furthermore, there seems to be a correlation between the levels of the two vitamin D metabolites, indicating that the regulation of $1,25(OH)_2$ vitamin D is not always tight, notably in persons with high BMI.

1. Introduction

Vitamin D is provided to the body either through photosynthesis in the skin or through absorption from ingested foods or supplements. It gets biologically active through hydroxylations [1]. The 25-hydroxylation step takes place mainly in the liver, and results in the formation of 25(OH) vitamin D (hereafter shortened to 25(OH)D). Once formed, 25(OH)D is released to the blood and carried to target cells for a second hydroxylation. Thus, $1,25(OH)_2$ vitamin D ($1,25(OH)_2D$) is formed. It is a major regulatory hormone of the calcium homeostasis. The main production site of $1,25(OH)_2D$ is the kidney and its synthesis is regulated by serum calcium, phosphorus, parathyroid hormone (PTH) and $1,25(OH)_2D$ itself [1].

In most determinations of the vitamin D status, the level of 25(OH)D is measured. This is done for two main reasons: firstly, vitamin D is fast taken up from the circulation and deposited mainly in adipose and muscular tissues [2,3]. Secondly, under certain conditions the level of $1,25(OH)_2D$ can give a misleading assessment of the vitamin D status, since its synthesis is increased as a consequence of even a mild 25(OH)D deficiency through a parathormone (PTH)-mediated regulatory loop [2,3].

Recently, increased attention has been focused on 25(OH)D, since its serum level seems to be associated with decreased risk and improved prognosis of several chronic diseases [4–7]. It has been recognized that many tissues, both normal and pathological ones, express the vitamin D receptor (VDR), and are in this way able to use 25(OH)D for modulation of complex biological functions [8]. The receptor affinity of 25(OH)D is approximately 100 times lower than that of 1,25(OH)D [9,10], but the serum levels are approximately 1000 higher, so a low affinity is partially compensated by a high availability. This may explain the clinical correlations mentioned above.

We have found that the prognosis of a number of internal cancers is dependent on season of diagnosis and therapy start, being best for summer and autumn [11–15]. Since the serum level of 25(OH)D is highest in these seasons, we have proposed that this vitamin D metabolite may act as an adjuvant in therapy, and have discussed possible mechanisms of action [11–15].

Following the classical theory of $1,25(OH)_2D$ synthesis and regulation, which is supported by several clinical investigations, there is generally no expected direct association between the serum levels of 25(OH)D and those of $1,25(OH)_2D$. Moreover, most studies of the seasonality of vitamin D metabolites show little or no correlation between sun exposure and $1,25(OH)_2D$ level, supporting the view that 1,25(OH)D formation is tightly regulated [16–21].

In the present study, we found that for persons with high BMIs the serum levels of $1,25(OH)_2D$ vary with season and seem to be associated with the levels of 25(OH)D. The effect of body mass index (BMI), age and gender on these associations have also been investigated.

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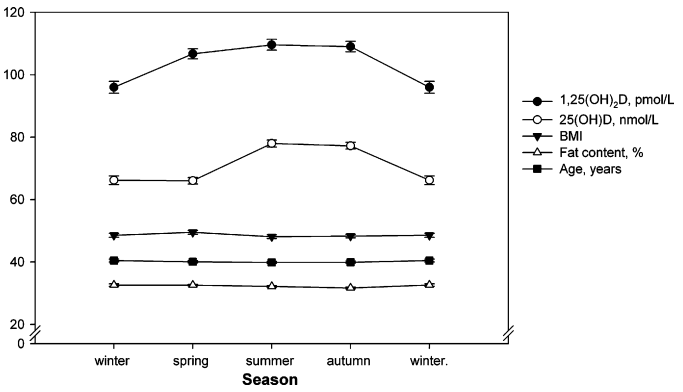

Fig. 1. Seasonal variations of 25(OH)D and 1,25(OH)$_2$D. BMI, fat content, and age were similar for the persons included in each season (bottom curves).

2. Materials and methods

Data on serum 25(OH)D and 1,25(OH)$_2$D levels for 2126 persons (1737 women and 389 men), and body composition (body mass index, height, weight, body fat mass) were provided by Dr. Fedon Lindberg's Clinic (a metabolic and medical lifestyle management clinic) in Oslo, Norway. The database also contains data on age, gender, main and secondary diagnosis. The first diagnosis for most of the persons was varying degree of obesity (62%) and overweight (27%), often associated with type 2 diabetes mellitus (6.5%) and metabolic syndrome (3.5%). The main goal of the treatment was usually weight loss through multidisciplinary lifestyle management. The database does not contain records on vitamin D intake or supplementation. If present, supplementation was done with vitamin D3 derivatives since Norway has no tradition of using D2 compounds [22].

Blood tests were routinely analyzed at the Hormone Laboratory, Aker University Hospital and Fürst Laboratories. Serum 25(OH)D levels were analyzed by high-performance liquid chromatography

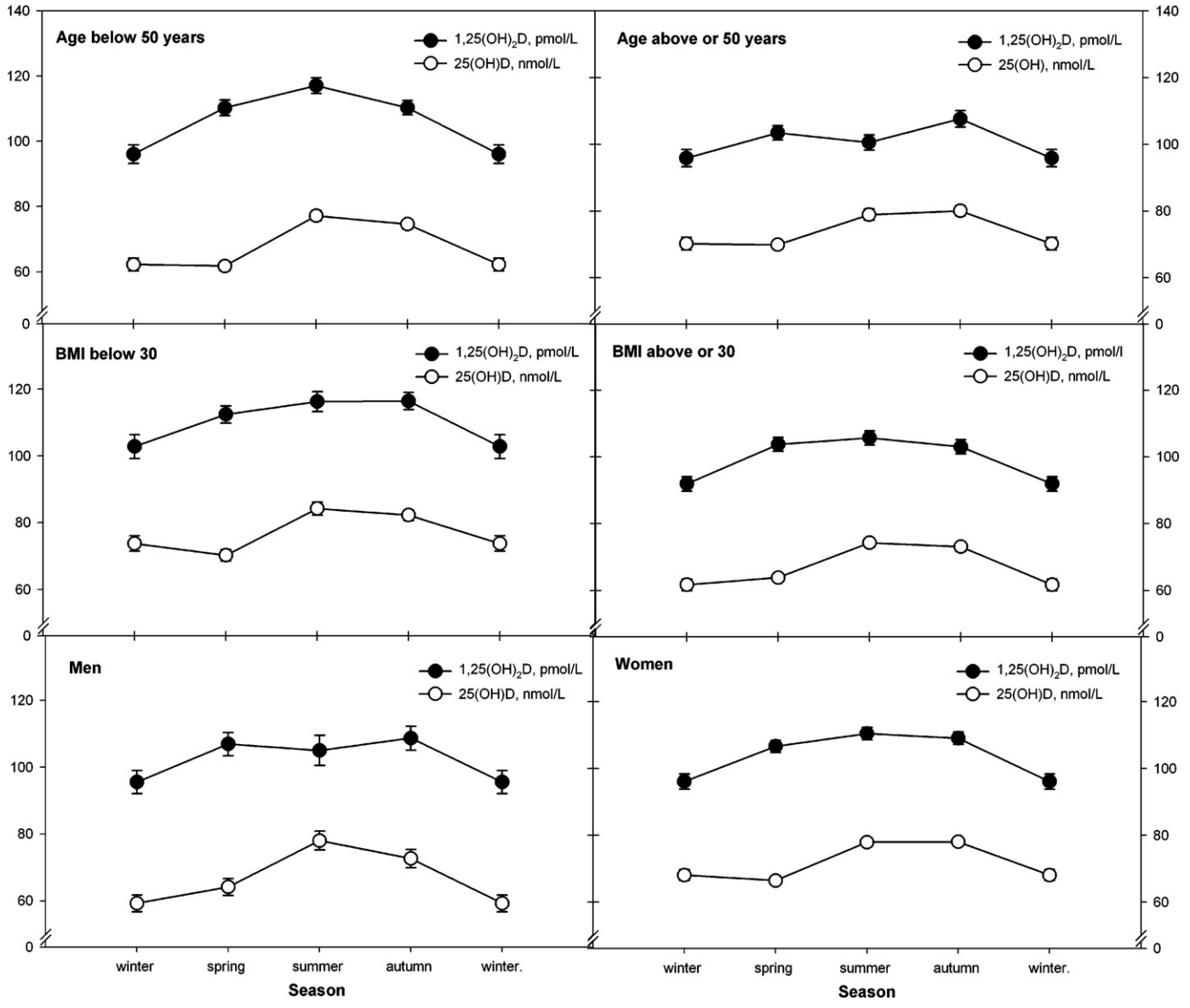

Fig. 2. Top: Seasonal variations of the two vitamin D metabolites for persons below and above 50 years of age. Middle: Seasonal variations for persons with BMIs below and above 30. Bottom: Seasonal variations for men and women separately.

with an inter-assay variation of 12% as precisely described by Falch et al. [23].

Serum 1,25(OH)$_2$D were measured using competitive radioimmunoassays (RIA) (DiaSorin, Stillwater, MN, USA). The inter-assay variation was between 8 and 12.5% for the levels of 0–60, 60–240 and 240–480 pmol/L and 17–20% for levels of 74, 140 and 340 pmol/L, respectively.

BMI and other parameters of body composition were estimated with Tanita Body Fat Monitors, TBF 300 GS (Tanita Corp of America, USA).

Based on time points of blood sampling the data were grouped in four groups: winter (1 December–28 February), spring (1 March–31 May), summer (1 June–31 August) and autumn (1 September–30 November). The seasonal variation of serum 25(OH)D and 1,25(OH)$_2$D was defined as the difference between winter and summer values.

The data were stratified for further analyses in age groups (cut-off point 50 years) and BMI groups (cut-off at 30). The cut-off of 50 years was chosen based on the theory that pre- and postmenopausal women may have differences in vitamin D metabolism due to hormonal changes and decreased levels of estrogens, shown to regulate expression and activity of 25 hydroxy-vitamin D-1alpha hydroxylase [24].

3. Results

Fig. 1 shows the seasonal variation of serum 25(OH)D and 1,25(OH)$_2$D in both men and women of all ages and BMI groups. The mean values of 25(OH)D and 1,25(OH)$_2$D were significantly lower during the winter than during the summer season ($p < 0.001$). The amplitude of the seasonal variation of 1,25(OH)$_2$D (15%) was similar to that of 25(OH)D (17%). Furthermore, Fig. 1 confirms that average age, BMI and body adiposity were similar for all seasonal measurements, in agreement with our expectations.

When the data were split into two age groups (<50 years and ≥50 years, Fig. 2, top panel), it turned out that the amplitudes of the seasonal variations for younger persons were 21% for 1,25(OH)$_2$D and 22% for 25(OH)D, which are about twice as large as those for older individuals. Moreover, the time points for the highest levels of both 25(OH)D and 1,25(OH)$_2$D for older persons seem to be slightly shifted towards the autumn compared with those for younger persons.

Fig. 2, middle panel, presents the BMI-dependency of the seasonal variations. Persons with high BMIs had lower serum levels of 25(OH)D and of 1,25(OH)$_2$D throughout the year than persons with low BMIs.

The data for men and for women were similar, although the seasonal variation seemed to be slightly larger for men than for women (Fig. 2, bottom panel).

Fig. 3 shows the seasonal variation of 1,25(OH)$_2$D separately for persons with insufficient (<75 nmol/L) and sufficient (≥75 nmol/L) levels of 25(OH)D. The figure shows that persons with sufficient 25(OH)D levels had significantly higher levels of 1,25(OH)$_2$D and a smaller seasonal variation (about 6.5%) than those with insufficient 25(OH)D levels (16.5%; $p < 0.001$). Thus, there is a positive correlation between 25(OH)D and 1,25(OH)$_2$D, and the amplitude of the seasonal variation of 1,25(OH)$_2$D depends on the initial (winter) levels, being largest for the lowest levels.

Figs. 4 and 5 show data from the literature on the seasonal variations of the two vitamin D metabolites, as functions of latitude and age. These data are included for the discussion.

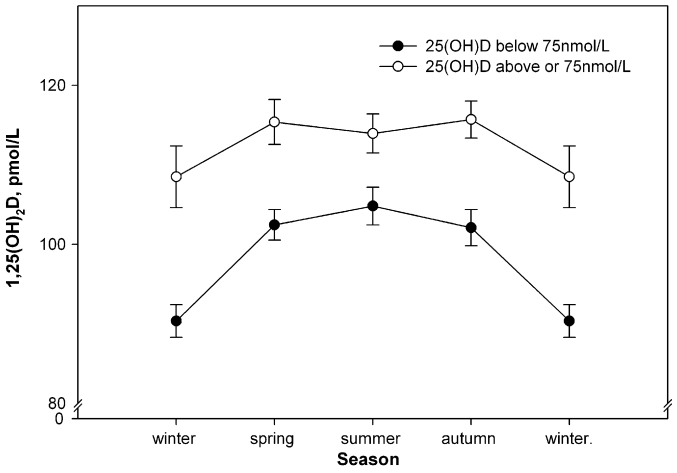

Fig. 3. Seasonal variations of 1,25(OH)$_2$D for persons with 25(OH)D levels above and below 75 nmol/L, respectively.

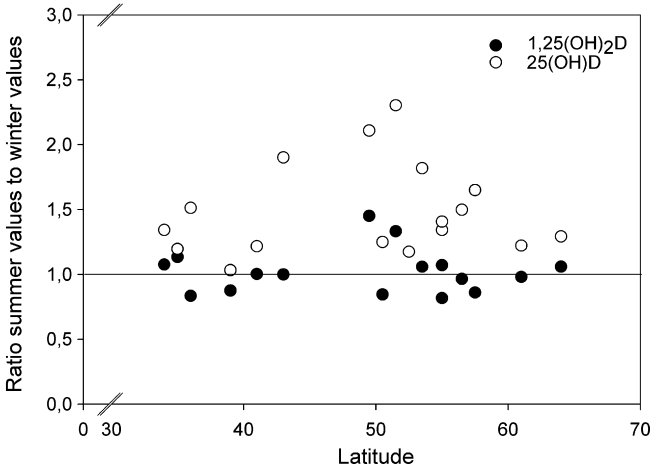

Fig. 4. Ratios of summer to winter values of 1,25(OH)$_2$D and 25(OH)D reported for different latitudes in different reports [17,19–21,34–45].

4. Discussion

There are two main sources of vitamin D for humans: food intake and photosynthesis in the skin. More than 90% of the circulating vitamin D in humans is produced in the skin by exposure to solar

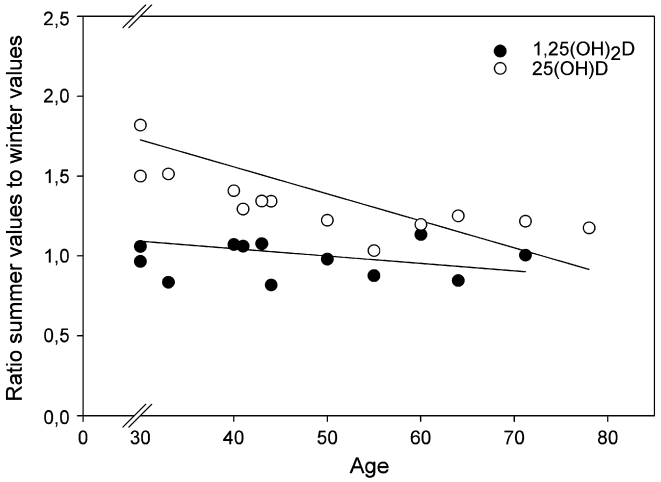

Fig. 5. Ratios of summer to winter values of 1,25(OH)2D and 25(OH)D for persons of different age, as given in different reports in the literatures [17,19–21,34–45].

ultraviolet B radiation (UVB) [2,25]. Since the daily fluence of UVB reaching the ground varies strongly through the year, a seasonal variation of the vitamin D status is expected and observed in most studies (Fig. 4). Commonly, the vitamin D status is assessed by quantifying the serum levels of 25(OH)D. The levels of $1,25(OH)_2D$ are usually not applied for clinical purposes since they are usually strictly regulated [26], often independently of the levels of 25(OH)D, and most investigations show no significant seasonal variations (Fig. 4).

We have analyzed data from 2126 persons treated in a clinic of metabolic diseases in Oslo, Norway. Surprisingly, we found a positive correlation between the serum levels of 25(OH)D and those of $1,25(OH)_2D$. Moreover, the levels of $1,25(OH)_2D$ had a similar seasonal variation as those of 25(OH)D. Thus, our findings show that in this population of persons with high BMI the synthesis of $1,25(OH)_2D$, the most active form of vitamin D, depends on the availability of its substrate, 25(OH)D. It may also depend on the activity of the renal enzyme 1-alfa hydroxylase [27–29].

There are some weak points in the present study. The levels of the vitamin D metabolites were measured only once per person, so we cannot follow seasonal changes of the vitamin D status on an individual basis. However, the large sample size and constancy of the values for average age, BMI and body adiposity for the different seasonal determinations (Fig. 1), indicate that our procedure is acceptable. An important parameter, which should have been taken into account, is the serum level of PTH, since this hormone is involved in the regulation of the vitamin D metabolism and may stimulate formation of $1,25(OH)_2D$ in the kidneys [26]. Unfortunately, PTH values were not available to us. Secondary hyperparathyroidism and high levels of PTH are common among overweight and obese persons [27]. Several studies indicate increased PTH concentrations in elderly subjects [30]. Thus, one might assume that also in our investigation the serum levels of PTH among persons of high age and high BMI were higher than average levels.

Our study shows that $1,25(OH)_2D$ levels are lower in obese and elderly persons. For obese persons this may be explained by low levels of 25(OH)D (substrate deficiency), as a consequence of its decreased bioavailability [31]. In elderly, 25(OH)D values were to our surprise higher than in young persons. However, this is in agreement with our earlier findings [11,13,15]. This is unexpected since the efficiency of the photosynthesis of vitamin D in human skin decreases with age [32]. Nevertheless, other factors may explain this discrepancy: food habits and awareness of the possibility of vitamin D deficiency may be different for different age groups, and there may be a low activity of the renal 1-alfa hydroxylase or a lower stimulatory effect of PTH on this enzyme in old than in young persons [33].

Similar trends with respect to the $25(OH)D/1,25(OH)_2D$ ratios were found by Parikh et al. in a large cohort study of healthy adults [27]. These investigators found, not only a positive correlation between the two metabolites, but also a dependency of the ratio on BMI and body adiposity. Thus, persons with high BMIs tended to have low levels of both 25(OH)D and $1,25(OH)_2D$, independently of the levels of PTH. Also another report shows a positive correlation between the two vitamin D metabolites, and even the lowest values during the winter [34]. This is surprising since the investigation was carried out in Israel, where the seasonal variation of UVB is smaller than in Norway. Such seasonal variations of $1,25(OH)_2D$ have been found in a few other studies as well, although most studies show no, or even an opposite variation, with highest levels of $1,25(OH)_2D$ in the winter (Fig. 4). This figure indicates no latitudinal dependency of the ratios. Such a dependency might be expected in view of the decreasing amplitude of the seasonal variation of UVB with decreasing latitude. However, most of the cited studies had small study populations, and no reliable conclusion about latitudinal dependency can be drawn.

Several recent reports support our data and indicate that formation of $1,25(OH)_2D$ may depend on substrate concentration [27,34,35]. Furthermore, although most investigations indicate no, or even a negative seasonal variation of $1,25(OH)_2D$, a few researchers have reported a positive one (Fig. 4) [17,19–21,34–45]. Clearly, this variation is smaller than that found for 25(OH)D by the same investigators.

As judged from literature data, as well as from our data, the seasonal variation of 25(OH)D seems to be largest for the youngest persons (Figs. 2 and 5). The same trend may seem to hold also for $1,25(OH)_2D$.

Acknowledgements

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References

[1] M.F. Holick, Vitamin D: photobiology, metabolism and clinical application, in: I.M. Arias, J.L. Boyer, N. Fausto, W.B. Jakoby, D. Schachter, D.A. Shafritz (Eds.), The Liver: Biology and Photobiology, Raven Press, New York, 1994, pp. 543–562.
[2] J.S. Adams, T.L. Clemens, J.A. Parrish, M.F. Holick, Vitamin-D synthesis and metabolism after ultraviolet irradiation of normal and vitamin-D-deficient subjects, N. Engl. J. Med. 306 (1982) 722–725.
[3] N.H. Bell, S. Epstein, A. Greene, J. Shary, M.J. Oexmann, S. Shaw, Evidence for alteration of the vitamin D-endocrine system in obese subjects, J. Clin. Invest. 76 (1985) 370–373.
[4] J.J. Cannell, R. Vieth, J.C. Umhau, M.F. Holick, W.B. Grant, S. Madronich, C.F. Garland, E. Giovannucci, Epidemic influenza and vitamin D, Epidemiol. Infect. 134 (2006) 1129–1140.
[5] B. Littorin, P. Blom, A. Scholin, H.J. Arnqvist, G. Blohme, J. Bolinder, A. Ekbom-Schnell, J.W. Eriksson, S. Gudbjornsdottir, L. Nystrom, J. Ostman, G. Sundkvist, Lower levels of plasma 25-hydroxyvitamin D among young adults at diagnosis of autoimmune type 1 diabetes compared with control subjects: results from the nationwide Diabetes Incidence Study in Sweden (DISS), Diabetologia 49 (2006) 2847–2852.
[6] K.L. Munger, L.I. Levin, B.W. Hollis, N.S. Howard, A. Ascherio, Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis, JAMA (2006) 2832–2838 (%20;296).
[7] A. Zittermann, Vitamin D and disease prevention with special reference to cardiovascular disease, Prog. Biophys. Mol. Biol. 92 (2006) 39–48.
[8] A.S. Dusso, A.J. Brown, E. Slatopolsky, Vitamin D, Am. J. Physiol Renal Physiol. 289 (2005) F8–28.
[9] P.F. Brumbaugh, M.R. Haussler, 1 Alpha, 25-dihydroxycholecalciferol receptors in intestine. I. Association of 1 alpha,25-dihydroxycholecalciferol with intestinal mucosa chromatin, J. Biol. Chem. 249 (1974) 1251–1257.
[10] W.S. Mellon, H.F. DeLuca, An equilibrium and kinetic study of 1,25-dihydroxyvitamin D3 binding to chicken intestinal cytosol employing high specific activity 1,25-dehydroxy[3H-26, 27] vitamin D3, Arch. Biochem. Biophys. 197 (1979) 90–95.
[11] Z. Lagunova, A.C. Porojnicu, A. Dahlback, J.P. Berg, T.M. Beer, J. Moan, Prostate cancer survival is dependent on season of diagnosis, Prostate 67 (2007) 1362–1370.
[12] J. Moan, A.C. Porojnicu, T.E. Robsahm, A. Dahlback, A. Juzeniene, S. Tretli, W. Grant, Solar radiation, vitamin D and survival rate of colon cancer in Norway, J. Photochem. Photobiol. B 78 (2005) 189–193.
[13] A.C. Porojnicu, T.E. Robsahm, A. Hansen Ree, J. Moan, Season of diagnosis is a prognostic factor in Hodgkin lymphoma: a possible role of sun-induced vitamin D, Br. J. Cancer 93 (2005) 571–574.
[14] A.C. Porojnicu, T.E. Robsahm, A. Dahlback, J.P. Berg, D.C. Christiani, O.S. Bruland, J. Moan, Seasonal and geographical variations in lung cancer prognosis in Norway: does vitamin D from the sun play a role? Lung Cancer 55 (2007) 263–270.
[15] A.C. Porojnicu, Z. Lagunova, T.E. Robsahm, J.P. Berg, A. Dahlback, J. Moan, Changes in risk of death from breast cancer with season and latitude: sun exposure and breast cancer survival in Norway, Breast Cancer Res. Treat. 102 (2007) 323–328.
[16] H. Li, M.J. Stampfer, J.B. Hollis, L.A. Mucci, J.M. Gaziano, D. Hunter, E.L. Giovannucci, J. Ma, A prospective study of plasma vitamin D metabolites, vitamin D receptor polymorphisms, and prostate cancer, PLoS Med. (2007), doi:10.1371/journal.pmed.0040103.
[17] R.A. Bouillon, J.H. Auwerx, W.D. Lissens, W.K. Pelemans, Vitamin D status in the elderly: seasonal substrate deficiency causes 1,25-dihydroxycholecalciferol deficiency, Am. J. Clin. Nutr. 45 (1987) 755–763.

[18] E.A. Krall, N. Sahyoun, S. Tannenbaum, G.E. Dallal, B. wson-Hughes, Effect of vitamin D intake on seasonal variations in parathyroid hormone secretion in postmenopausal women, N. Engl. J. Med. 321 (1989) 1777–1783.
[19] R.W. Chesney, J.F. Rosen, A.J. Hamstra, C. Smith, K. Mahaffey, H.F. DeLuca, Absence of seasonal variation in serum concentrations of 1,25-dihydroxyvitamin D despite a rise in 25-hydroxyvitamin D in summer, J. Clin. Endocrinol. Metab. 53 (1981) 139–142.
[20] L. Tjellesen, C. Christiansen, Vitamin D metabolites in normal subjects during one year. A longitudinal study, Scand. J. Clin. Lab Invest. 43 (1983) 85–89.
[21] T.J. Hine, N.B. Roberts, Seasonal variation in serum 25-hydroxy vitamin D3 does not affect 1,25-dihydroxy vitamin D, Ann. Clin. Biochem. 31 (1994) 31–34.
[22] H.E.Meyer, L.Brunvand, M.Brustad, K.Holvik, L.Johansson, J.E.Paulsen, Tiltak for å sikre en god vitamin D status i Befolkningen [action for achieving a good vitamin D status in the population], 2006, Ref Type: Report.
[23] J.A. Falch, H. Oftebro, E. Haug, Early postmenopausal bone loss is not associated with a decrease in circulating levels of 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, or vitamin D-binding protein, J. Clin. Endocrinol. Metab. 64 (1987) 836–8341.
[24] D. Somjen, S. Katzburg, N. Stern, F. Kohen, O. Sharon, R. Limor, N. Jaccard, D. Hendel, Y. Weisman, 25 Hydroxy-vitamin D(3)-1alpha hydroxylase expression and activity in cultured human osteoblasts and their modulation by parathyroid hormone, estrogenic compounds and dihydrotestosterone, J. Steroid Biochem. Mol. Biol. 107 (2007) 238–244.
[25] M.F. Holick, Vitamin D: a millenium perspective, J. Cell Biochem. 88 (2003) 296–307.
[26] M.F. Holick, Vitamin D status: measurement, interpretation, and clinical application, Ann. Epidemiol. (2008).
[27] S.J. Parikh, M. Edelman, G.I. Uwaifo, R.J. Freedman, M. Semega-Janneh, J. Reynolds, J.A. Yanovski, The relationship between obesity and serum 1,25-dihydroxy vitamin D concentrations in healthy adults, J Clin. Endocrinol. Metab. 89 (2004) 1196–1199.
[28] L. Rejnmark, P. Vestergaard, L. Heickendorff, L. Mosekilde, Plasma 1,25(OH)2D levels decrease in postmenopausal women with hypovitaminosis D, Eur. J. Endocrinol. 158 (2008) 571–576.
[29] M.S. Barnes, M.P. Bonham, P.J. Robson, J.J. Strain, A.S. Lowe-Strong, J. Eaton-Evans, F. Ginty, J.M. Wallace, Assessment of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D3 concentrations in male and female multiple sclerosis patients and control volunteers, Mult. Scler. 13 (2007) 670–672.
[30] R. Malik, Vitamin D and secondary hyperparathyroidism in the institutionalized elderly: a literature review, J. Nutr. Elder 26 (2007) 119–138.
[31] J. Wortsman, L.Y. Matsuoka, T.C. Chen, Z. Lu, M.F. Holick, Decreased bioavailability of vitamin D in obesity, Am. J. Clin. Nutr. 72 (2000) 690–693.
[32] J. MacLaughlin, M.F. Holick, Aging decreases the capacity of human skin to produce vitamin D3, J. Clin. Invest. 76 (1985) 1536–1538.
[33] H.J. Armbrecht, M.A. Boltz, C.S. Ritter, A.J. Brown, Parathyroid hormone stimulation of the renal 25-hydroxyvitamin D-1alpha-hydroxylase—effect of age and free radicals, J. Steroid Biochem. Mol. Biol. 103 (2007) 330–333.
[34] E. Kristal-Boneh, P. Froom, G. Harari, J. Ribak, Seasonal changes in calcitropic hormones in Israeli men, Eur. J. Epidemiol. 15 (1999) 237–244.
[35] J.R. Juttmann, T.J. Visser, C. Buurman, E. de Kam, J.C. Birkenhager, Seasonal fluctuations in serum concentrations of vitamin D metabolites in normal subjects, Br. Med. J. (Clin. Res. Ed.) 282 (1981) 1349–1352.
[36] K. Landin-Wilhelmsen, L. Wilhelmsen, J. Wilske, G. Lappas, T. Rosen, G. Lindstedt, P.A. Lundberg, B.A. Bengtsson, Sunlight increases serum 25(OH) vitamin D concentration whereas 1,25(OH)2D3 is unaffected. Results from a general population study in Goteborg, Sweden (The WHO MONICA Project), Eur. J. Clin. Nutr. 49 (1995) 400–407.
[37] A.G. Need, H.A. Morris, M. Horowitz, C. Nordin, Effects of skin thickness, age, body fat, and sunlight on serum 25-hydroxyvitamin D, Am. J. Clin. Nutr. 58 (1993) 882–885.
[38] K. Overgaard, L. Nilas, J.S. Johansen, C. Christiansen, Lack of seasonal variation in bone mass and biochemical estimates of bone turnover, Bone 9 (1988) 285–288.
[39] A. Porojnicu, T.E. Robsahm, J.P. Berg, J. Moan, Season of diagnosis is a predictor of cancer survival. Sun-induced vitamin D may be involved: a possible role of sun-induced Vitamin D, J. Steroid Biochem. Mol. Biol. 103 (2007) 675–678.
[40] P.B. Rapuri, H.K. Kinyamu, J.C. Gallagher, V. Haynatzka, Seasonal changes in calciotropic hormones, bone markers, and bone mineral density in elderly women, J. Clin. Endocrinol. Metab. 87 (2002) 2024–2032.
[41] L. Rejnmark, M.E. Jorgensen, M.B. Pedersen, J.C. Hansen, L. Heickendorff, A.L. Lauridsen, G. Mulvad, C. Siggaard, H. Skjoldborg, T.B. Sorensen, E.B. Pedersen, L. Mosekilde, Vitamin D insufficiency in Greenlanders on a westernized fare: ethnic differences in calcitropic hormones between Greenlanders and Danes, Calcif. Tissue Int. 74 (2004) 255–263.
[42] D. Rucker, J.A. Allan, G.H. Fick, D.A. Hanley, Vitamin D insufficiency in a population of healthy western Canadians, CMAJ 166 (2002) 1517–1524.
[43] S.S. Sherman, B.W. Hollis, J.D. Tobin, Vitamin D status and related parameters in a healthy population: the effects of age, sex, and season, J. Clin. Endocrinol. Metab. 71 (1990) 405–413.
[44] H. Yamashita, T. Murakami, S. Noguchi, M. Shiiba, S. Watanabe, S. Uchino, H. Kawamoto, M. Toda, N. Murakami, Postoperative tetany in Graves disease: important role of vitamin D metabolites, Ann. Surg. 229 (1999) 237–245.
[45] A. Zittermann, K. Scheld, P. Stehle, Seasonal variations in vitamin D status and calcium absorption do not influence bone turnover in young women, Eur. J. Clin. Nutr. 52 (1998) 501–506.