VITAMIN D STATUS:
UV-EXPOSURE, OBESITY AND CANCER

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ABBREVIATIONS *(in alphabetical order)*

1,25(OH)₂D	1,25-Dihydroxyvitamin D
25(OH)D	25-Hydroxyvitamin D
7-DHC	7-Dehydrocholesterol
BB-UVB	Broadband Ultraviolet B
BCa	Breast Cancer
BMD	Bone Mineral Density
BMI	Body Mass Index
CD	Crohn's disease
CIE	The International Commission on Illumination
CLIA	Chemiluminescent Immunoassay
CMM	Cuteneous Malignant Melanoma
CRC	Colorectal Cancer
CYP24A1	24-hydroxylase
CYP27B1	1ɑ-hydroxylase
CYP2R1	25-hydroxylase
DBP	Vitamin D binding protein
E-BSA	Exposed Body Surface Area
ECa	Endometrial Cancer
FGF23	Fibroblast Growth Factor-23
GWAS	Genome-Wide Association Study
HPLC	High-Performance Liquid Chromatography
IU	International Units
LC-MS	Liquid Chromatography-Mass Spectrometry
MED	Minimal Erythema Dose
MS	Multiple Sclerosis
mVDR	Membrane vitamin D receptor
NB-UVB	Narrowband Ultraviolet B
NIST	National Institute of Standards and Technology
nVDR	Nuclear vitamin D receptor
OR	Odds Ratio
PCa	Prostate Cancer
PTH	Parathyroid hormone
RA	Rheumatoid Arthritis
RCT	Randomized Clinical Trial
RDD	Recommended daily dose for vitamin D intake
RIA	Radio-Immunoassay
RR	Relative risk

RXR	Retinoic X Receptors
Sun_1	Sun bed – Life Sun S 100W
Sun_2	Sun bed – Solarium Super Plus 100 W
Sun_3	Sun bed – Golden Sun RS 100 W + Beauty Sun 25 W
SDD	Standard vitamin D dose
SED	Standard erythema dose
sHPT	Secondary Hyperparathyroidism
SLE	Systemic Lupus Erythematosus
SPF	Sun Protection Factor
SZA	Solar Zenith Angle
T1D	Type 1 Diabetes
TUL	Tolerable Upper Limit
UVA	Ultraviolet A (320-400nm)
UVB	Ultraviolet B (280-320 nm)
UV_{D3}	Previtamin D_3 weighted UV
UV_{Ery}	Erythema weighted UV
UVI	Ultraviolet Index
UVR	Ultraviolet Radiation
VDDS	Vitamin D Deficiency Syndrome
VDRE	Vitamin D-Responsive Element
DEQAS	Vitamin D External Quality Assessment Scheme

RELEVANT UNITS AND CONVERSIONS

$1,25(OH)_2D$: Concentration [pmol/L] $\quad = 2.4$ x Concentration [pg/ml]

$25(OH)D$: Concentration [nmol/L] $\quad = 2.5$ x Concentration [ng/ml]

SED: Dose [J/m^2] $\quad = 0.1$ x Dose [mJ/cm^2]

Vitamin D intake: Dose [IU] $\quad = 40$ x Dose [μg]

FACTS ABOUT VITAMIN D

VITAMIN D: VITAMIN D_3 (cholecalciferol) and VITAMIN D_2 (ergocalciferol)

Vitamin D, the "sunshine vitamin", is a fat-soluble steroid pro-hormone. Vitamin D is a biologically inert compound, and has to undergo a number of conversions in order to become an active hormone. The main source of vitamin D_3 for humans is sun exposure. Another important source for vitamin D is food. Vitamin D_3 is present in few animal foods, mainly fat fish, while vitamin D_2 is found in some wild mushrooms. Both vitamin D forms are available in supplements. The high dose supplementation available in Norway is a vitamin D_2 form.

25-HYDROXYVITAMIN D (CALCIDIOL or 25(OH)D)

Vitamin D, produced in the skin or obtained from food and supplements, undergoes its first hydroxylation in the liver and becomes 25(OH)D. Serum 25(OH)D is the major form of vitamin D and the most reliable determinant of vitamin D status. Serum 25(OH)D concentrations reflect well the cutaneous vitamin D synthesis and ingested vitamin D. According to the classification proposed by M.F. Holick, one of the world leaders in vitamin D research, vitamin D deficiency should be defined as serum 25(OH)D levels < 50 nmol/L, vitmin D insufficiency as 50-74 nmol/L, and vitamin D sufficiency as values ≥ 75 nmol/L.

1,25-DIHYDROXYVITAMIN D (CALCITRIOL or 1,25(OH)$_2$D)

In the kidneys 25(OH)D undergoes the second hydroxylation to 1,25(OH)$_2$D. Serum 1,25(OH)$_2$D is an active steroid hormone that regulates calcium homeostasis and bone mineralization. Vitamin D status can not be determined by 1,25(OH)$_2$D measurements, since its serum concentrations are tightly regulated and may remain normal even in the setting of vitamin D deficiency. The 1,25(OH)$_2$D signaling pathway is mediated through the vitamin D receptor (VDR). Almost 40 tissues in the human body express VDR. Thus, it has been recently proposed that 1,25(OH)$_2$D may be involved in regulation of many physiological functions.

LIST OF PUBLICATIONS

1. **Lagunova Z.**, Porojnicu A.C., Grant W.B., Bruland Ø., Moan J. Obesity and increased risk of cancer: Does decrease of serum 25-hydroxyvitamin D level with increasing body mass index explain some of the association? Mol Nutr Food Res 2010; 54(8):1127-33.

2. **Lagunova Z.**, Porojnicu A.C., Vieth R., Lindberg FA., Hexeberg S., Moan J. The serum 25-hydroxyvitamin D is a predictor of 1,25-dihydroxyvitamin D in overweight and obese patients. J Nutr. 2011; 141(1):112-7.

3. **Lagunova Z.**, Porojnicu A.C., Lindberg F.A., Aksnes L., Moan. J.Vitamin D status in Norwegian children and adolescents with excess body weight. Pediatr Diabetes. 2011; 12(2):120-6.

4. Moan J., **Lagunova Z.**, Cicarma E., Aksnes L., Dahlback A., Grant W.B., Porojnicu A.C. Sunbeds as vitamin D sources. Photochem Photobiol. 2009; 85(6):1474-9.

5. **Lagunova Z**, Porojnicu AC, Aksnes L., Holick M.F., Iani V., Bruland Ø., Moan J., Effect of vitamin D supplementation and ultraviolet B exposure on serum 25-hydroxyvitamin D concentrations in healthy volunteers. (submitted)

1. ABSTRACT

Sun is the main vitamin D source for humans. Sun exposure during the summer may provide large amounts of vitamin D_3, which is stored in the fat tissue and released during the winter. Serum 25(OH)D levels > 80 nmol/L at the end of the summer are considered necessary in order to avoid vitamin D deficiency during the winter. However, it is not clear how much sun exposure is needed to achieve this concentration. In this study we simulated a Norwegian summer by using commercially available tanning equipment. We found that moderate exposures given during 5-7 weeks may raise serum 25(OH)D concentrations from typical winter values to typical summer values. A UV dose equal to a whole body sun exposure of 5 - 10 MED at sunny summer midday increased serum 25(OH)D by 15-23 nmol/L. The increase was dependent on the initial vitamin D status: persons with the lowest baseline 25(OH)D concentrations got the largest increase. However, for persons with vitamin D deficiency (25(OH)D < 50 nmol/L) the mentioned UV exposure was not large enough to reach the threshold of vitamin D sufficiency (25(OH)D ≥ 75 nmol/L). Moreover, a daily whole body sun exposure of ~0.2 MED seems to be almost equal to an oral vitamin D intake of 2,000 IU.

Body composition and BMI are important predictors of vitamin D status. Our earlier investigations suggested that serum 25(OH)D levels decrease proportionally with increasing BMI. The key mechanism behind is possibly increased sequestration of fat-soluble vitamin D in a large volume of fat tissue. However, other factors, such as low sun exposure and inadequate vitamin D intake, may also contribute to the low vitamin D status in overweight and obese persons. In this study we have investigated the impact of excess body weight on serum $1,25(OH)_2D$ concentrations. According to our results high BMI and adiposity in adults were associated with decreased serum $1,25(OH)_2D$. Serum 25(OH)D was the strongest predictor of $1,25(OH)_2D$ values. A decrease in 25(OH)D by 1 nmol/L was associated with a decrease in $1,25(OH)_2D$ concentrations by 0.4 pmol/L (P<0.001). There was no correlation between serum concentrations of 25(OH)D and $1,25(OH)_2D$ in obese children and adolescents, although the prevalence of vitamin D deficiency and insufficiency in adolescents was high (58 %).

Low vitamin D status as a consequence of low sun exposure and/or high BMI may play a role in cancer development and prognosis. Our calculations suggest that a low vitamin D status may explain at least 20% of the cancer risk attributable to high BMI. It also seems that the contribution of low 25(OH)D to the increased cancer risk with increasing BMI may be different for different cancer types being highest for colorectal and breast cancers.

A panel of 25 world leaders in vitamin D research recommended that the serum 25(OH)D concentrations should be at least ≥ 75 nmol/L (30 ng/ml) in order to provide optimal health outcomes. These values may be achieved by moderate UV exposure or by high vitamin D intake. The dose of vitamin D supplementation and UV exposure should be adjusted according to BMI.

2. AIMS OF THE STUDY

The objective of this study was to investigate the complex association between vitamin D predictors (UV exposure, BMI, vitamin D intake), serum 25(OH)D concentrations, and cancer risk.

In order to investigate the effect of UV exposure on serum 25(OH)D concentrations a Norwegian summer was simulated by using commercially available tanning equipment during the winter. Thus, our aims were:

- ❖ to investigate the effect of moderate UV exposure on vitamin D status
- ❖ to investigate the impact of initial vitamin D status on serum 25(OH)D increase
- ❖ to investigate the role of body weight and vitamin D intake on serum 25(OH)D increase
- ❖ to compare the efficiency of high dose vitamin D supplementation and moderate UV exposure to increase serum 25(OH) concentrations

To determine the association between excess body weight, vitamin D status, and serum $1,25(OH)_2D$ concentrations we analyzed a data base containing relevant data for almost 1,900 adults and children with overweight and obesity. We aimed to:

- ❖ investigate the prevalence of vitamin D deficiency and insufficiency
- ❖ estimate the associations between body composition, BMI, age, gender, and serum concentrations of 25(OH)D and $1,25(OH)_2D$
- ❖ investigate the association between serum $1,25(OH)_2D$ and 25(OH)D
- ❖ study the seasonal variation of both serum 25(OH)D and $1,25(OH)_2D$

Furthermore, we wanted to investigate if low vitamin D status related to high BMI plays any role in cancer development. We aimed to:

- ❖ estimate the possible contribution of vitamin D to cancer risk attributable to high BMI

3. VITAMIN D SYNTHESIS AND METHABOLISM

Vitamin D, also known as the "sunshine vitamin", is a fat-soluble steroid pro-hormone. It is available in two distinct forms: cholecalciferol (Vitamin D_3) and ergocalciferol (vitamin D_2) (**Figure 1**) (1).

The main source of vitamin D_3 for humans is sun (2). About 90-95% of total vitamin D is produced in the skin (3). Another important source for vitamin D is food (4). Vitamin D_3 is present in few animal foods, mainly fat fish, while vitamin D_2 is found in some wild mushrooms (4). Both vitamin D forms are available in supplements. Although in a number of studies vitamin D_3 has proven to be the most potent form for humans, both vitamin D forms are still regarded as equivalent and interchangeable (5).
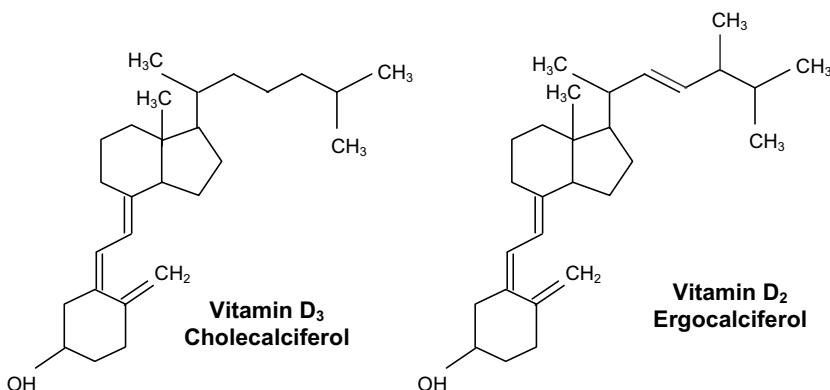
Figure 1. Two distinct forms of vitamin D

3.1. Cutaneous vitamin D_3 synthesis

Exposure of uncovered skin to ultraviolet B radiation (UVB) (280-320 nm) generates previtamin D_3 from 7-dehydrocholesterol in the plasma membranes of the cells in upper skin layers, mainly in the stratum basale and the stratum spinosum (3;6). Previtamin D_3 undergoes a rapid thermal isomerization to vitamin D_3. Once formed, vitamin D_3 is ejected out of the plasma membrane into extracellular space, where it enters the bloodstream and binds to vitamin D binding protein (DBP) (3).

The concentrations of previtamin D_3 in the skin reaches its maximum within hours, however it may take 24-48 hours to few days until serum vitamin D levels increase (7). Under prolonged UVB exposure both previtamin D_3 and vitamin D_3 can be converted to several biologically inactive photoproducts, mainly lumisterol and tachysterol (8). These compounds may also be converted back when the concentrations of previtamin D_3 decreases. Thus, excessive sun exposure does not result in vitamin D intoxication (8).

3.2. Vitamin D metabolism

Vitamin D is a biologically inert compound, and has to undergo a number of conversions in order to become an active hormone (3;6). In the blood stream vitamin D and its metabolites are bound to DBP that plays an important role in maintaining vitamin D status (**Figure 2**) (9).

3.2.1. From a vitamin to an active hormone. DBP transports vitamin D to the liver where it undergoes the first hydroxylation to 25-hydroxivitamin D (25(OH)D) catalysed by one or more cytochrome P450 vitamin D 25-hydroxylases (CYP2R1, CYP27A1) (10). Other cytochrome P450 enzymes may also be involved in vitamin D 25-hydroxylation (11;12). Genetic variations of CYP2R1 may influence serum 25(OH)D concentrations (13). In the blood steam 25(OH)D binds to DBP to be transported to the kidneys and other tissues. In the kidneys 25(OH)D undergoes a second hydroxylation to 1,25-dihydroxyvitamin D (1,25(OH)$_2$D) by 1α-hydroxylase (CYP27B1) (10). The renal expression of CYP27B1 is up-regulated by parathyroid hormone (PTH), low serum calcium, and high phosphates concentrations, and down-regulated by fibroblast growth factor 23 (FGF 23) and high 1,25(OH)$_2$D (12;14). At the same time, low PTH, high calcium, and low phosphates concentrations stimulate expression of 24-hydroxylase (CYP24A1), an enzyme that catabolizes both 25(OH)D and 1,25(OH)$_2$D to calcitroic acid (11).
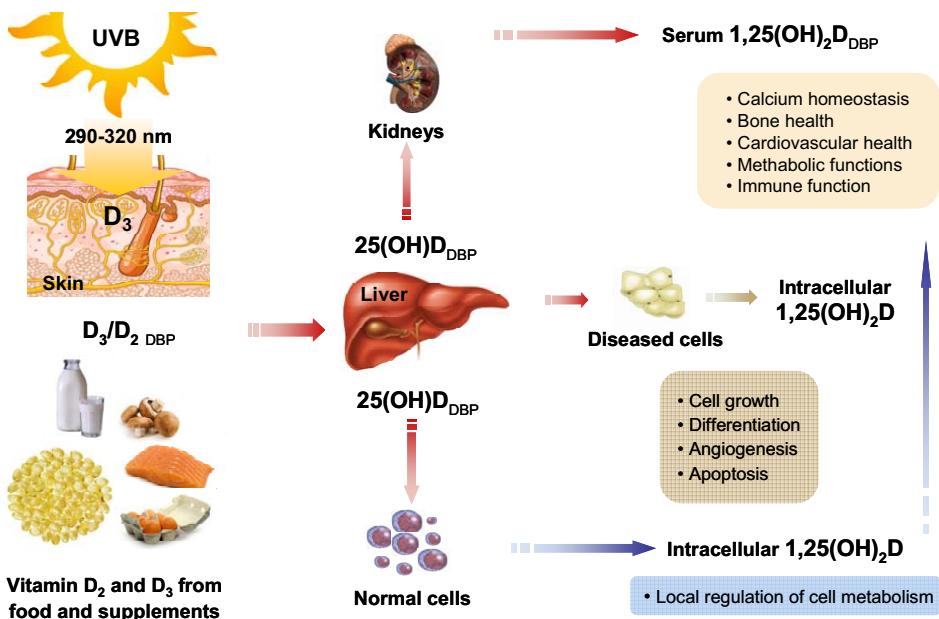
Figure 2. Vitamin D sources and metabolism.

Although, CYP27B1 is found predominantly in kidneys, it is also expressed by many other cell types, such as macrohages, T-lymphocytes, dendritic cells, keratinocytes, bone, placenta and prostate cells (15;16). Several types of cancer cells (intestine, prostate, lung, skin etc.) may also convert 25(OH)D to $1,25(OH)_2D$ (10;16). It has recently been revealed that a few cell types (keratinocytes, macrophages, prostate epithelial cells, osteoblasts) may metabolize vitamin D to $1,25(OH)_2D$ (10).

3.2.2. The role of DBP in vitamin D metabolism. In the blood circulation vitamin D metabolites are bound to DBP and to other proteins (9). The main functions of DBP are solubilization and transport of vitamin D metabolites to target tissues. Binding to DBP decreases the bioavailability of vitamin D active metabolites, and, possibly, prevents vitamin D intoxication (17). It may also preserve vitamin D metabolites from fast catabolism, thus, increasing their half-life time. In this case, DBP acts as a reservoir for vitamin D circulating forms. Serum DBP concentrations are 100-fold higher than those of 25(OH)D, and only 5% of DBP binding sites are occupied by vitamin D methabolites (17). The binding affinity of DBP is different for each vitamin D metabolite, and is highest for 25(OH)D. Approximately 88% of serum 25(OH)D, 85% of serum $1,25(OH)_2D$, but only 60% of vitamin D are bound to DBP (17;18). DBP is a highly polymorphic protein (19). Genetic variants of DBP have been associated with large differences in binding affinity to vitamin D ligands, and may explain much of the interpersonal variation in the levels circulating 25(OH)D and $1,25(OH)_2D$ (20). DBP polymorphism also predicts response of serum 25(OH)D to vitamin D supplementation and sun exposure (13;19;21).

3.3. Mechanisms of vitamin D action

$1,25(OH)_2D$ is transported from the kidneys by DBP to organs and tissues where it acts in both genomic or non-genomic manner (10;22) Vitamin D signaling is mediated through vitamin D receptor that may be located in the cell nucleus (nVDR) or the cell membrane (mVDR) (22). Almost 40 tissues express one or both types of VDR (22), and about 3% of the human genome may be regulated by $1,25(OH)_2D$ (23).

3.3.1. Genomic vitamin D response is mediated through nVDR and takes hours or even days (10;22). VDR is functioning as a heterodimer and commonly recruits retinoid X receptor (RXR). VDR-RXR heterodimers build complexes with co-regulatory proteins that further interact with specific genomic sequences, vitamin D response elements (VDRE), in the promoter region of target genes (10;22).

The study by Ramagopalan et al. on lymphoblastoid cell lines provides a high-resolution map of VDR binding throughout the human genome, and indicates 2776 binding sites and 229 genes that can be up- or down-regulated in response to $1,25(OH)_2D$ stimulation (24). The VDR binding activity was high around the genes that, according to recent genome-wide association studies (GWAS) were associated with multiple sclerosis (MS), diabetes type 1 (T1D), Crohn's disease (CD), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), chronic lymphocytic leukemia, colorectal cancer, hair color, tanning, and height (**Figure 3**) (24;25). Interestingly, VDR binds more actively to the regions responsible for positive selection (hair color, skin sensitivity). This suggests an important role of vitamin D in human evolution (24). Although these data strongly support pleiotropic vitamin D activities, further research is needed to identify the particular molecular mechanisms behind vitamin D action.

VDR activation regulates the expression of at least 11 genes essential for calcium homeostasis and bone health including SPP1 (osteopontin), TRPV6 (selective calcium channel), LRP5 (low density lipoprotein receptor-related protein 5), BGP, RANKL (receptor activator for nuclear factor κ B ligand), OPG (osteoprotegerin), CYP24A1, PTH, FGF23, PHEX (phosphate-regulating gene) and klotho protein (26).

3.3.2. Non-genomic vitamin D responses are probably mediated through mVDR (27). The non-genomic mechanism of action include activation of protein kinase C (PKC), mitogen-activated protein kinase (MAPK), phosholipase A_2 (PLA$_2$), phospholipase C (PLC), G-protein and opening of ion channels (22). The time required for non-genomic effects may vary from a few seconds to 10-60 minutes (22).
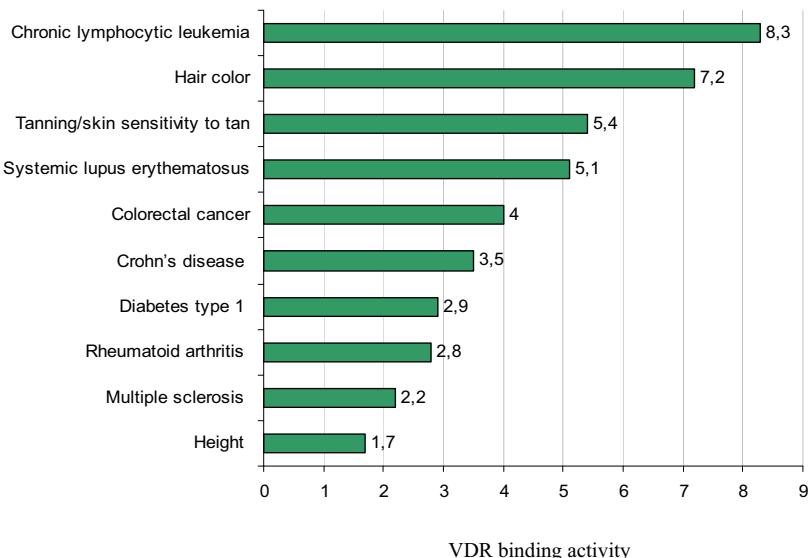
Figure 3. VDR binding activity around the genes related to common diseases identified by recent genome-wide association studies (GWAS) (24).

The effects of vitamin D are commonly subdivided as classical and non-classical (8;28). The main classical role of 1,25(OH)$_2$D is to maintain mineral homeostasis and bone health by increasing the absorption of calcium and phosphates in intestine and reabsorption in kidneys, regulation of serum PTH and FGF23 levels, and control of bone growth, mineralization and remodeling (29;30).

Among non-classical vitamin D actions may be listed inhibition of cell proliferation and induction of differentiation, regulation of innate and anti-bacterial immune responses and control over hormone secretion (8). These mechanisms explain the essential role of vitamin D in muscle function, cardiovascular homeostasis, nervous function, immune, endocrine, and circulatory systems (31)

4. VITAMIN D SOURCES

Vitamin D may be obtained from UVB exposure (sun, tanning units, narrowband, and broadband UVB lamps) and dietary intake (unfortified and fortified foods and supplements).

4.1. Sun and artificial UVB sources

Sun is definitely the cheapest, the most available and the most natural vitamin D source among all possible sources of UVB (32). However, it is probably not the most efficient one. Broadband and narrowband UVB cabinets for psoriasis treatment, as well as some tanning units commercially available in Europe, seem to be more efficient sources for vitamin D, if one takes into account shorter irradiation times and larger body area that can be exposed at the same time.

The main differences between sun and artificial UVB sources are intensity and proportional content of UVB, ultraviolet A (UVA) (320-400nm), and visible light (**Figure 4**). These basic differences may have impacts on health effects of UV radiation, including vitamin D synthesis.
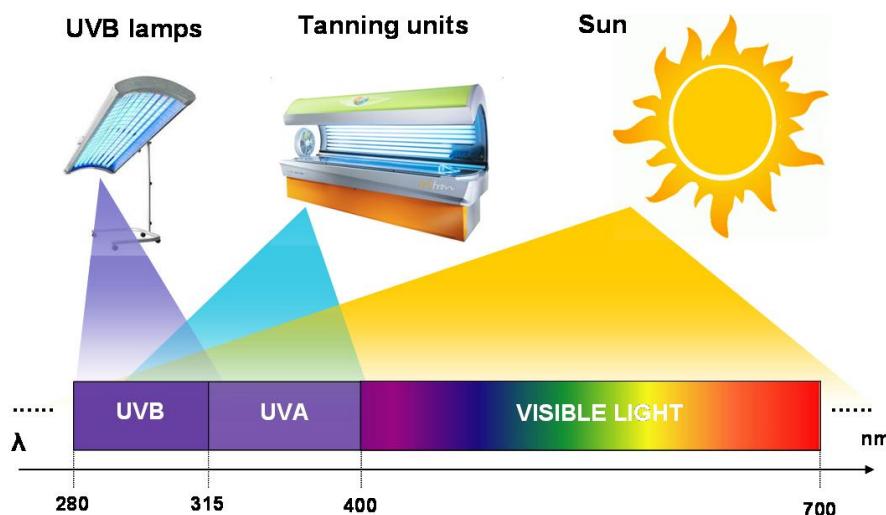
Figure 4. Sources of UVB radiation.

4.1.1. Erythema- and vitamin D- weighted UV. Even short exposures to the sun may produce a large amount of vitamin D_3 (33). UV exposure of the whole body to one minimal erythema dose (MED) seems to increase serum vitamin D_3 levels equivalent with an oral dose of 10,000-20,000 IU (3).

4.1.1.1. Minimal erythema dose (MED) is defined as the minimal UV dose required to produce perceptible erythema (a slight pinkness) to the skin as determined 24 hours after

exposure to UV source (34). MED can be expressed in minutes or in UV dose (J/m^2), adjusted to the International Commission on Illumination (CIE) recommended action spectra for erythema (35). The MED is an individual and often subjective indicator of skin sensitivity to UV radiation. It varies with skin pigmentation, skin type, UV intensity and other factors (36). Therefore, standardized MED for each skin type were developed (**Table 1**).

4.1.1.2. Standard erythema dose (SED). Due to very high interindividual variations of MED it is not always convenient to describe the UV doses in MED, especially in large populations, at different latitudes and with different UV sources. Thus, SED is more often used to describe occupational and controlled UV exposure as well as effects of different UV doses on human health, including cutaneous vitamin D_3 synthesis (37). The SED equals to 100 J/m^2 weighted by CIE erythema action spectrum and the emission spectrum of the UV source (37). Thus, the SED is a more accurate measure of physical UV exposure than MED.

Table 1. MED and SED in different skin types (34;38)

Skin type	Reaction to sun	MED (J/m^2)	MED (min)*	SED
I	Always burns; never tans	200	22	2
II	Burns easily; tans minimally	250	28	2.5
III	Burns moderately; tans gradually	300	33	3
IV	Rarely burns; tans easily	450	50	4.5
V	Very rarely burns; tans substantially	600	67	6
VI	Never burns; deeply pigmented	1000	111	10

* Oslo, 12:00 a.m. 22 June 2010, 1 SED = 11 minutes

4.1.1.3. UV index (UVI) is another important measure of UVR (32). UVI is calculated by the formula: $\mathbf{UVI = 40 \times UV_{Ery}}$, where UV_{Ery} is CIE erythema weighted UV (W/m^2) (39). UVI are usually presented as a scale from 1 to 15 that indicates the risk level of possible skin damage due to UV exposure. Based on UV index, the number of SED achieved per hour can be calculated (SED h^{-1}) (**Figure 5**) (32).

4.1.1.4. Standard vitamin D dose (SDD). To estimate the efficiency of UV source to induce vitamin D_3 synthesis it has been also proposed to use vitamin D weighted UV dose (UV_{D3}) and SDD (33). UV_{D3} dose may be calculated as the area under the curve obtained by multiplication of CIE vitamin D action spectrum and the emission spectrum of the UV source (**Figure 6**) (40;41). The ratio between UV_{D3} and UV_{Ery} indicates the benefit/risk balance, and shows the efficiency of light source to induce vitamin D synthesis during certain erythema dose (42).

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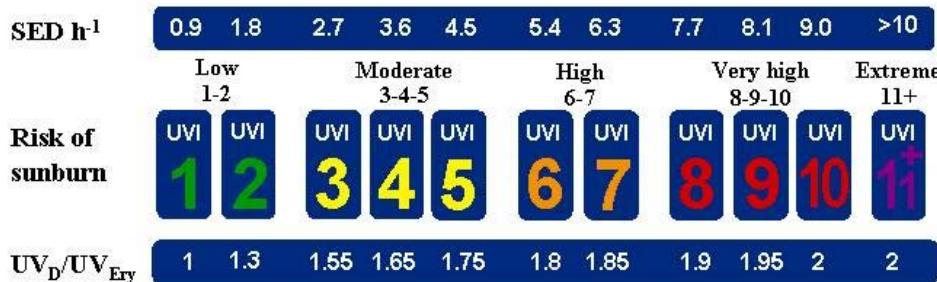
Figure 5. Range of UVI and corresponding exposure for erythema (SED h^{-1}) and vitamin D synthesis for skin type II (32)

The SDD is defined as the UV dose necessary for a serum vitamin D_3 increase equal to an oral vitamin D dose of 1000 IU (33). According to Holick, SDD may be achieved by a UV exposure of ¼ skin area (hands, face and arms) to ¼ of personal MED (33). The SDD is in a way a similar measure as MED for erythema, but only for vitamin D synthesis. Thus, it feels right to suggest a measure similar to SED, which will reflect a fixed dose of CIE vitamin D weighted UV. According to the results of our recent study, a vitamin D weighted UV dose of about 100 J/m^2 may possibly be as effective to improve vitamin D status as an oral vitamin D_3 dose of 2000 IU (43). Thus, a dose of 100 J/m^2 of vitamin D weighted UV may be a good candidate dose for proposed measure. For Oslo sun this dose will be equal to ~0.6 SED of whole body exposure.
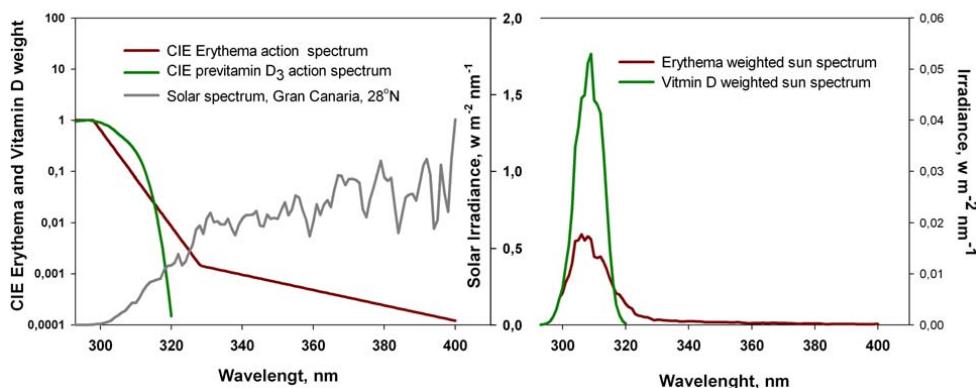
Figure 6. Action spectra of erythema, previtamin D_3, and sun in Gran Canaria (left panel). Efficiency spectra for vitamin D synthesis and erythema production (right panel).

4.1.2. Efficiency of vitamin D synthesis. The effectiveness of UV sources to induce vitamin D_3 synthesis depends on UVB fluence rates, ratio between vitamin D weighed (UV_{D3}) and erythema weighed UV (UV_{Ery}) (UV_{D3}/ UV_{Ery}) and skin pigmentation (1;38;44-47).

Solar UVB fluence rates, as well as UV_{D3}/ UV_{Ery}, vary with latitude, season, weather conditions and day time (1;48;49). Thus, an optimal benefit to risk condition for vitamin D synthesis from solar UV exposure occurs under high solar altitude, low zenith angle, midday midsummer sunlight (42).

Artificial sources of UV radiation include various lamps used both in medicine (psoriasis broadband and narrowband UVB lamps) and industry (sun bed lamps). According to state regulations, only type 3 sun beds are commercially available in Norway (50). The regulations limit the CIE erythema weighted UV to 0.3 W/m^2 (0.15 W/m^2 of UVB and 0.15 W/m^2 of UVA) (50). The intensity of broadband and narrow band UVB lamps used to treat psoriasis is 3-15-fold higher than that (51). The efficiency of artificial UV sources to induce vitamin D synthesis may be estimated based on UV_{D3}/ UV_{Ery} that varies between 0.5 and 2 depending on lamp type (42). The tanning units used in our studies had $UV_{D3}/ UV_{Ery} = 1.3$ (43;52). The UV doses for sun at different latitudes and tanning units used in the study are compared in **Table 2**.

Table 2. UV doses of different UVB sources for the skin type II person (33;38;51).

UV source	MED (min)	SED (min)	UV_{D3} per SED (J/m^2)	$UV_{D3}/$ UV_{Ery}	SDD (min)
Oslo Sun*	28	11	170	1.70	7
Gran Canaria Sun*	15	6	187	1.87	4
Equator Sun*	11	4.3	188	1.88	3
Tanning device Sun$_2$[1]	23	9	125	1.25	6
Tanning devise Sun$_3$[2]	15	6	134	1.34	4

* 11 a.m.-13 p.m. June 2010
[1] Solarium Super Plus 100 W
[2] Golden Sun RS 100W combined with Beauty Sun S 25 W

4.2. Food and supplements

2.1. Food sources. There are only few foods that naturally contain vitamin D. Fatty fish (mackerel, salmon, herring) and cod liver oil are the major sources of vitamin D_3 in Norway (**Table 3**) (53). Small amounts of vitamin D_3 are also present in beef liver, eggs and meat (4). Some dairy products in Norway including butter, margarine, and milk are fortified with vitamin D_3 (53). Vitamin D_2 is found in wild mushrooms and plants (4).

Table 3. Vitamin D content in unfortified and fortified foods

Food	µg	IU	%RDD*	%TUL**
Fish meal, 150g portion				
Fish liver (cod)	72.4	2900	725	145
Mackerel (salmon, traut, herring)	17.5	700	175	35
Cod roe	5.3	212	53	11
Cod, saithe, haddock	3.0	120	30	6
Fish soup, gratin	2.4	96	24	4.8
Fish fingers, breaded	2.0	80	20	4
Catfish	0.7	28	7	1.4
Sandwich spread, 25 g				
Roe paste	6.0	240	60	12
Sardines, herring, sprat	3.0	120	30	6
Smoked salmon	1.4	56	14	2.8
Mackerel	1.3	50	13	2.5
Butter, margarine, 10 g	0.8	32	8	1.6
Milk (extra light), 1.5 dl	0.6	24	6	1.2
Bakery products, cakes, 1 pc	0.4	16	4	0.8
Egg, 1 pc	0.36	14	4	0.7

*Recommended Daily Dose (RDD) in Norway is 400 IU
** Tolerable Upper Limit (TUL) for daily vitamin D intake is 2,000 IU

4.2.2. In supplements vitamin D is available in both forms: vitamin D_3 and vitamin D_2. Although, there are mainly vitamin D_3 supplements that are used in Norway (**Table 4**) (53). Cod liver oil (Tran) is traditionally one of the most popular vitamin D supplements in Norway with 60% of adult population using it (54).

Table 4. Vitamin D content in supplements

Supplements	μg	IU	%RDD*	%TUL**
Vitamin D_3				
Cod liver oil (Tran[1]), 5ml	10	400	100	20
Cod liver oil (Tran capsules), 1 cp	5	200	50	10
Nycoplus D-vitamin (tablets) 1 tab	10	400	100	20
Nycoplus D-vitamin (drops), 5 dr	10	400	100	20
Waifa- Calcium 500 mg + D-vitamin, 1 tab	10	400	100	20
Calcigran forte Calcium 500 mg + D, 1 tab	10	400	100	20
Sanasol, 5 ml	5	200	50	10
Spektro multi (tablets), 1 tab	2.5	100	25	5
Vitamin D_2				
AFI-D 2 forte[2] (capsules), 1 cp	750	30000	1070[2]	214[2]

*Recommended Daily Dose (RDD) in Norway is 400 IU
** Tolerable Upper Limit (TUL) for daily vitamin D intake is 2,000 IU
[1]Tran produced by different companies in Norway contains the same amount of vitamin D
[2]1 capsule per week is usually prescribed

4.2.3. The daily recommended vitamin D intake (RDD) in Norway is 7.5 μg (300 IU) for adults, and 10 μg (400 IU) for children (6-23 months) and persons > 60 years (54). These recommendations are similar to those in other European countries (55). Vitamin D supplementation is usually recommended during the winter months when vitamin D_3 can not be produced in the skin (56).

   The upper tolerable limit for vitamin D intake (UTL) (maximum daily intake unlikely to cause any health risks) is set to 2,000 IU (50 μg) for adults and at 1,000 IU (25 μg) for children (55;57). However, it has been shown that vitamin D daily intake of doses <10,000 IU does not result in any sign of toxicity (9).

   Based on a report from National Nutrition Council (56), the intake of vitamin D with food in Norway is in the range of 3 to 6 μg/d, slightly lower in women (4.0 μg) than in men (5.8 μg). The total vitamin D intake (including supplements) is of the order of 4 to 14 μg/d

(56). The contribution of vitamin D supplements, unfortified and fortified foods to mean daily vitamin D intake in Norway seems to be the following: 45%, 30% and 25%, respectively (53). There is a large variation of daily vitamin D intake between different age groups, with the lowest intake among teenagers (58). Significantly higher vitamin D intake was observed in northern Norway compared to southern of Norway (56;58;59). That is probably due to high consumption of cod liver oil and fish including *mølje* (a traditional north Norwegian fish meal consisting of cod liver) (59). One *mølje* meal may provide the equivalent of 7-18 RDD (59).

Although, Norway has few foods fortified with vitamin D_3, it has one of the highest daily vitamin D intakes in Europe (60). Traditions of fish eating and high cod liver oil consumption might have contributed to that.

5. VITAMIN D STATUS

Vitamin D, produced in the skin or obtained from food and supplements, is a biologically inert compound, and is, therefore, not routinely measured in routine clinical practice (61). Although $1,25(OH)_2D$ is the most active vitamin D metabolite, serum **25(OH)D** is the most abundant form of vitamin D and the most reliable determinant of vitamin D status (3;9;62). Serum 25(OH)D concentrations reflects the cutaneous vitamin D synthesis and ingested vitamin D well (3;10). Serum $1,25(OH)_2D$ concentrations are about 0.01% of 25(OH)D values, and are in most cases strictly regulated by PTH, calcium and phosphate (3;61). Therefore, serum $1,25(OH)_2D$ is usually not considered for assessment of the vitamin D status. However, it may be a useful estimation in patients with kidney diseases and very low serum 25(OH)D (62).

5.1. Measurements of vitamin D status

There are many commercially available assays for vitamin D measurements. However, their comparability is uncertain (63). High-pressure liquid chromatography (HPLC) was considered as a "gold standard" for vitamin D status assessment, however, now it is not often used routinely (64;65). Radioimmunoassay (RIA) for 25(OH)D measurements was developed in 1985, and became one of the most common methods for routine 25(OH)D evaluation (64;66;67). Other common methods are liquid chromatography-tandem mass spectrometry (LC−MS), chemiluminescent immunoassays (CLIA), enzyme immunoassays, competitive protein binding assays, and automated chemiluninescence protein-binding assays (66).

A recent study compared three available assays: HPLC-APCI-MS (HPLC-atmospheric pressure ionization-mass spectrometry), RIA (IDS, UK) and CLIA (LIAISON, Diasorin) (**Figure 7**) (63). In the same set of samples the mean 25(OH)D concentrations were 85 nmol/L, 70 nmol/L, and 60 nmol/L measured by HPLC, RIA and CLIA, respectively (63). Thus, the difference between HPLC and RIA values was 14.8 nmol/L, and between HPLC and CLIA – 24.5 nmol/L. Both HPLC-APCI-MS and CLIA were evaluated and approved by Vitamin D External Quality Assessment Scheme (DEQAS), a program aimed to improve reliability of 25(OH)D measurements (63;68).

Several other studies and data sets from DEQAS show large assay-specific variation (65-70). It is sometimes difficult to explain this variability, but it has been proposed that different methods may not recognize equally 25(OH)D$_2$, 25(OH)D$_3$ and some other recently discovered metabolites, such as 3-epi-25-hydroxyvitamin D (3-epi-25(OH)D) present in samples from infants (64;69). This may lead to both false-positive and false-negative results, and difficulties in clinical interpretation (64). The majority of methods have a tendency to underestimate the actual vitamin D status. Thus, a measured 25(OH)D $\geq$ 100 nmol/L may only ensure that the patient has serum 25(OH)D $\geq$ 80 nmol/L (67;69).

To guarantee the accuracy of available 25(OH)D assays the National Institute of Standards and Technology (NIST, USA) has recently developed a reference material for circulating 25(OH)D (SRM 972) (69). It consists of 4 pools of frozen serum with different concentrations of 25(OH)D$_2$, 25(OH)D$_3$, or both. The fourth pool additionally contains 3-epi-25(OH)D$_3$ (69).

Figure 7. Prevalence of vitamin D deficiency, insufficiency, and sufficiency in the same population according to HPLC, RIA, and CLIA measurements (63).

Thus, it seems possible to standardize the methods used in different laboratories to one reference material and get analysis certification by NIST. In the nearest future several methods will be validated according to the NIST procedure, and their reliability will be improved, but to date LC-MS/MS and HPLC seem to be the most reliable methods for 25(OH)D assessment (65;70;71). Although these methods require more expensive equipment and take considerably longer time, they provide accurate quantitative measurements of both 25(OH)D$_2$ and 25(OH)D$_3$ (71). Immunoassays may have enough sensitivity to recognize low vitamin D status, however, they may be imprecise in estimation of high serum 25(OH)D values (71). Some methods do not separate D$_2$ and D$_3$ forms and evaluate a sum of 25(OH)D$_2$ and 25(OH)D$_3$. These methods often have lower sensitivity for 25(OH)D$_2$ than for 25(OH)D$_3$, and underestimate the total 25(OH)D$_2$ (64;67;69;71). In cases when vitamin D$_2$ is not available in food or supplements, it may be of minor importance. In contrast, high dose supplementation (30,000 IU, AFI-D2 forte) available in Norway is a vitamin D$_2$ form, and the evaluation of the effect of supplementation may largely depend on the method chosen for serum 25(OH)D assessment.

5.2. Serum 25-hydroxyvitamin D concentrations

The lack of uniform terminology and classification system makes it very difficult to define the categories of vitamin D status. According a classification proposed by Holick, vitamin D deficiency should be defined as serum 25(OH)D levels < 50 nmol/L, vitmin D insufficiency as 50-74 nmol/L, and vitamin D sufficiency as values ≥ 75 nmol/L (**Figure 8**) (61). Other authors proposed different thresholds for vitamin D deficiency and insufficiency, but mainly setting the threshold at 50 nmol/L (27;72;73).

5.2.1. The cut-off for vitamin D deficiency was mainly chosen based on classical vitamin D actions on mineral homeostasis. Serum 25(OH)D levels < 50 nmol/L are associated with mineralization defects, such as rickets in infants and children and osteomalacia in adults. On the other hand, several studies suggest that levels < 80 nmol/L may be related to impaired calcium absorption, lower bone mineral density (BMD) and osteoporosis (74;75). Thus, the cut-off 50 nmol/L may be too low even in regard to bone health.

5.2.2. Recommended vitamin D status. A panel of 25 world famous vitamin D researchers recommended that the serum 25(OH)D concentrations should be at least ≥ 75 nmol/L (30 ng/ml) in order to provide optimal health outcomes (76). Since most of the methods underestimate serum 25(OH)D concentrations (67;69), choosing this cut-off ensures that the true 25(OH)D values are > 50 noml/L (67). Serum 25(OH)D levels < 75 nmol/L may be considered as low (72).

Figure 8. Vitamin D status (61).

The threshold of 75 nmol/L was chosen based mostly on two considerations: serum PTH concentrations and non-classical effects of vitamin D (76).

One of the main roles of PTH in vitamin D metabolism is to maintain serum 1,25(OH)$_2$D and calcium values in the normal range in the setting of low serum 25(OH)D concentrations. Serum 25(OH)D correlates negatively with serum PTH, and PTH increases with decreasing serum 25(OH)D (61). High PTH increases the activity of renal 1ά – hydroxylase that leads to increased 1,25(OH)$_2$D production by kidneys. However, secondary hyperpatathyroidism (sHPT) caused by low 25(OH)D may result in low BMD, osteoporosis and high risk of fractures (77). Serum 25(OH)D concentrations ≥ 75 nmol/L suppress serum PTH levels maximally and provide optimal calcium absorption (72;78). At the same time some studies reported different thresholds for maximal PTH suppression in the range between 50 and 80 nmol/L (79), and in some studies the relationship between serum 25(OH)D and PTH

appeared to be linear (80;81). These findings indicate that optimal range of serum 25(OH)D concentrations may differ between individuals. Moreover, racial differences in the relationship between vitamin D status, serum PTH and bone mineral density have been recently observed (79;80). A number of studies suggest that an optimal level of serum 25(OH)D may be different for Caucasians and non-Caucasians, since blacks increase PTH at 25(OH)D levels of about 50 nmol/L (79;80). Furthermore, blacks seem to need lower 25(OH)D levels to maintain normal BMD (80). This suggests evolutionary developed differences in calcium homeostasis between races. Thus, it may be inappropriate to extrapolate directly the cut-offs for vitamin D deficiency and optimal vitamin D status developed for whites to other races and ethnic groups (80).

Serum 25(OH)D concentrations > 75-80 nmol/L have been associated with decreased incidence of several common diseases, including cancer, autoimmune diseases, diabetes, cardiovascular events and total mortality (**Figure 9**) (76;82-91). These associations were proposed mainly on a basis of epidemiological studies of disease risk and outcomes in connection to pre-diagnostic vitamin D levels or surrogate measures of vitamin D status, such as UVB exposure and vitamin D intake (31;64;76). Experimental studies on cell lines and animal models support the hypothesis that the observed associations may by related to non-classical actions of vitamin D (16;23;92;93)
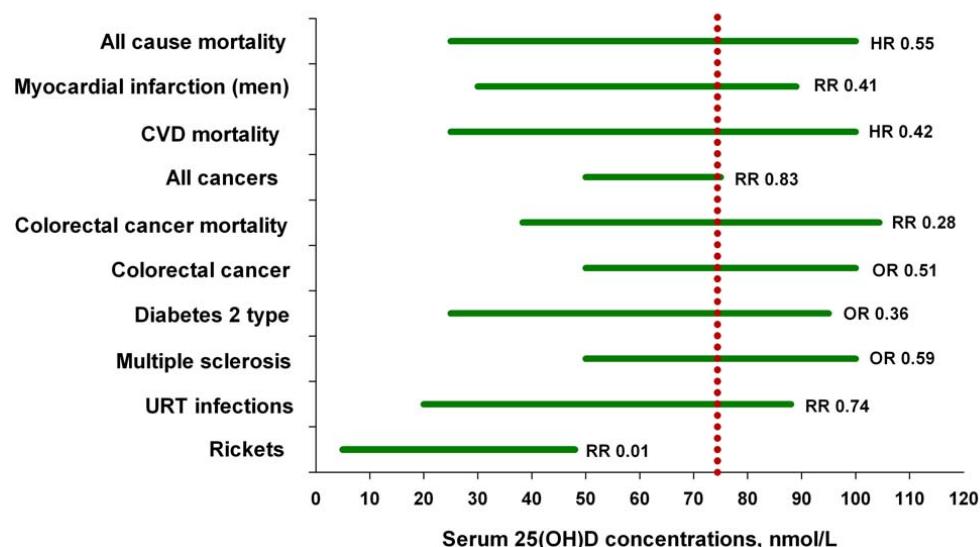
Figure 9. Disease incidence prevention by serum 25(OH)D in prospective studies (82-87;89-91;94).

The effects of vitamin D supplementation on common diseases were further investigated in several randomized clinical trials (RCT). However, many of these studies turned to be inconclusive, possibly because the dose of vitamin D supplementation was too low to cause any significant improvement of vitamin D status (76;95;96). Nevertheless, some recent RCT have proven the beneficial effects of vitamin D supplementations on total mortality (RR 0.93; CI, 0.87-0.96) (meta-analysis of 18 RCT) (97), risk of wintertime influenza A in nursery school children (RR 0.58; CI, 0.34-0.99) (98), prevention of non-vertebral fractures (RR 0.80; CI, 0.72-0.89) (meta-analysis of 9 RCT, dose- dependent effect) (99), cancer risk (RR 0.2; CI, 0.09-0.60) (Ca + D group) (100), risk of falls (RR 0.77; CI, 0.65-0.90) (101), and risk of cardio-vascular events (RR 0.90; CI, 0.77-1.05) (meta-analysis of 8 RCT) (102). In a large RCT on overweight and obese persons (103) vitamin D supplementation ameliorated symptoms of depression, but did not affect cardiovascular risk factors (104) and cytokine levels (105). Lack of effect of vitamin D supplementation on circulating cytokine levels was also reported by Yusupov et al. (106).

5.2.3. Vitamin D deficiency syndrome (VDDS). Since vitamin D deficiency is often observed in patients with osteoporosis, chronic fatigue, chronic pain, depression, autoimmune diseases, diabetes, heart diseases, hypertension and certain cancer types, some researchers proposed to define a combination of these conditions as VDDS (107). This does not necessary mean that these diseases are caused by vitamin D deficiency, or that administration of vitamin D will cure them (107). VDDS is most probably a multifactorial disease with many contributing factors, but improvement of vitamin D status may possibly reduce the symptoms of VDDS.

5.2.4. Toxic vitamin D status. Excessive UVB exposure does not cause any vitamin D intoxication, even though the exposure to 1 MED equals 10,000-25,000 IU of vitamin D supplementation (1;108). However, high doses of vitamin D supplementation (> 10,000 IU/d) may result in vitamin D intoxication associated with hypercalcemia (62;109;110). The most common symptoms of vitamin D intoxication are extreme pain due to kidney stone, vomiting, fever, chills, acute renal failure and any sings of dehydration related to hypercalcemia, such as conjunctivitis, increased thirst, constipation and hyporeflexia (109). The main biochemical findings of vitamin D intoxications are: hypercalcemia, hypercalciuria, secondary hypoparathyroidism and serum 25(OH)D concentrations > 280 nmol/L (109). The threshold serum 25(OH)D concentration for vitamin D toxicity, according to some researchers, may be in the range of 375-500 nmol/L (64;72). Moreover, few studies reported that a daily supplementation with 10,000 - 40,000 IU did not affect calcium methabolism, even though serum 25(OH)D may reach levels > 400 nmol/L (111-113).

5.3. Global vitamin D status

According to recent meta-analysis on 394 cross-sectional studies with 32,266 subjects included from all over the world, the mean serum 25(OH)D levels was 54 nmol/L (114). Based on a cut-off level of 75 nmol/L for serum 25(OH)D concentrations it has been estimated that over 80% of people, world-wide, have a low vitamin D status, and only 4 % were reported to have values >100 nmol/L (114). As it might be expected, Caucasians had higher 25(OH)D concentrations compared with non-Caucasians (**Figure 10**). The study also reported, significantly lower

serum 25(OH)D in children (<15 years) and older persons (>75 years) than in adults (15-75 years), and slightly higher values in women compared to men, 56 nmol/L vs. 50 nmol/L, respectively (114).
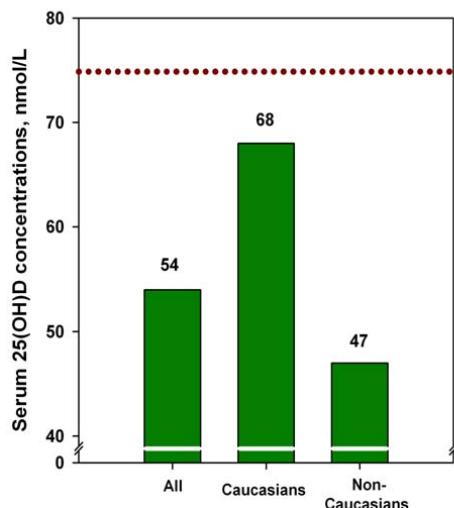
Figure 10. Global vitamin D status (114). Data are means serum 25(OH)D concentrations.

Depending on latitude, season, age and ethnical origin prevalence of vitamin D deficiency (serum 25(OH)D < 50 nmol/L) varies largely world-wide, being highest in non-Western developing countries (115;116).

Serum 25(OH)D < 25 nmol/L (severe vitamin D deficiency) were most common in Sub-Saharan Africa, South Asia and Middle East regions (115). Despite of high UVB rates, up to 50% of populations living in these regions have serum 25(OH)D below the cut-off of 25 nmol/L (116;117). Some studies from Mongolia, China, Libanon, and Iran report high prevalence of severe vitamin D deficiency (10-60%) with a cut-off of 12.5 nmol/L (116).

Although, vitamin D deficiency is less prevalent in Europe than in the above mentioned countries, the occurrence of serum 25(OH)D < 50 nmol/L was reported to be 40-80% (118). The best vitamin D status in Europe was observed in the Nordic countries, including Norway (115;116;118;119). The mean serum 25(OH)D concentrations in Norway have often been reported to be within the range of 60-80 nmol/L (56;59;120-124). The prevalence of vitamin D deficiency among native Norwegians is about 10-15 % (56), but may be as high as 40-50% during the winter (120). Teenagers and elderly generally have high rates of vitamin D deficiency (40-80%). Although, serum 25(OH)D concentrations < 25 nmol/L are rare among native Norwegians, non-Western immigrants from Pakistan, Sri Lanka, Vetnam, Turkey and Somalia have an average serum 25(OH)D levels of ~25nmol/L (121;123;124). Approximately 50-60 % of immigrants have concentrations < 25 nmol/L, and, in 10-15% of them the levels are < 12.5 nmol/L (121;124).

6. RISK FACTORS FOR LOW VITAMIN D STATUS

A number of factors may contribute to the development of vitamin D deficiency. Little sun exposure or sun avoidance together with low vitamin D intake are definitely the main reasons (61;72;125). However, in certain circumstances other factors may be equally important. Impaired vitamin D absorption from the intestine may result in vitamin D deficiency, even under adequate vitamin D supplementation (126). The same applies for persons with excess body weight, but due to other reasons than malabsorption (127;128). Older persons,

individuals with dark skin, and persons with severe chronic diseases and kidney failure are also at risk of vitamin D deficiency (61;72;76).

6.1. Sun exposure

Season, latitude, time of day, atmospheric conditions, skin pigmentation, and sun exposure habits (sun avoiding behavior, clothing, sunscreens use) are among the factors that may affect vitamin D synthesis in the skin (1).

6.1.1. Latitude and solar zenith angle. UVB fluence rates are highest at locations and times with low solar zenith angles (SZA), and decrease with increasing SZA (32;38;129;130). Thus, the UVB intensity is highest at equator, and lowest at northern latitudes (32). The UVB fluence and UV_{D3}/ UV_{Ery} also depend on ozone depletion (38). This means that higher amounts of vitamin D may be produced at the equator than at northern latitude (32;130).

One might then expect to find a geographical gradient in vitamin D levels. However, a recent meta-analysis of 394 cross-sectional studies on vitamin D status at different latitudes (0°-80^oN) showed no significant correlation between latitude and vitamin D status (114). It is worthwhile to mention that a north-south gradient before multiple adjustments was observed in Caucasians (114). Previous studies revealed contradictory results (77;131). A strong negative association between vitamin D status and latitude was observed by Zittermann et al. (131), and a positive one by Lips at al. (77).

The lack of latitude gradient in vitamin D status may be explained by differences in sun exposure habits, clothing, vitamin D intake from food and supplements, genetic factors, skin pigmentation, and methods used to determine vitamin D status (114).

6.1.2. Seasonal variation. At latitudes > 40° more UVB is absorbed by the ozone layer due to large SZA (46;130;132;133). Thus, much less UVB is reaching the ground. In Oslo vitamin D production from the sunlight takes place only during the summer months (April-October), since during the winter sunlight contains almost no UVB (46;134).

Due to this seasonal variation in annual UVB fluence rates, serum vitamin D levels also vary with the season (132;135;136). Highest vitamin D concentrations are observed between July and September, and lowest in February and March (120;128;132;137;138). The prevalence of vitamin D deficiency is high during the winter months (30-40 %), and in some groups of people, predisposed to low vitamin D, may reach 90-100 % (56;73). On the average, summer values are about 50% higher than winter concentrations, and normally are > 80 nmol/L (21;56;72;73;133;137;139-141). Several recent studies reported that winter serum 25(OH)D concentrations correlate positively with 25(OH)D values achieved at the end of the previous summer (138;140;142). Thus, it has been suggested that serum 25(OH)D concentrations > 80 nmol/L at the end of the summer are required to prevent against vitamin D deficiency (< 50 nmol/L) during the following winter (138;140). Moreover, summer values > 100 nmol/L may maintain the winter concentrations > 70 nmol/L (142). Some individuals have a low vitamin D status even during the summer (120;128;140). Sun avoidance, sunscreen use, clothing, little time spend outside and lack of clear recommendations for sun exposure may have contributed to the low vitamin D status in these individuals (138;140;143).

In order to achieve any optimal vitamin D status during the summer it has been recommended to expose 25 % of the body surface (hands, face and arms) to the sun in the

middle of the day to ¼ MED daily (33). However, this sun exposure can prevent only against vitamin D deficiency, and seems not to be enough to reach serum 25(OH)D concentrations > 75 nmol/L (40). On the other hand, an exposure to 1.4 SED (~0.5 MED) every day during the summer in real life conditions (summer clothing) may result in serum 25(OH)D levels >80 nmol/L (138). It has also been shown that women who spent on the average 4-6 hours every week outdoor during summer reached the serum 25(OH)D levels ~100 nmol/L (142). Working outdoors was also associated with a good vitamin D status at the end of the summer (**Table 6. Part I**) (144;145).

Vacations to sunny countries may improve vitamin D status significantly, especially during winter months (142;146). In the study by Osmancevic et al. serum 25(OH)D increased by almost 50 nmol/L after 15 days of climate therapy of psoriasis patients at Gran Canaria (146). Thus, after whole body exposure of total dose 166 SED serum 25(OH)D levels were on the average 105 nmol/L (146).

6.1.3. Atmospheric conditions. A number of environmental factors may attenuate the fluence of UVB radiation, including total ozone, clouds, aerosols, surface reflectivity and low altitude (48;147-149). Thick cloud cover and ozone layer may reduce vitamin D synthesis even considerably at the equator (48). Snow cover may increase vitamin D production, since it reflects and scatters a large fraction of UVB (48). Most calculations for vitamin D synthesis are still performed for clear atmospheric conditions (148). Usually, planar horizontal geometry is used, but we have shown that vertical cylinder geometry will give different and more realistic results (46).

Air pollution may also be associated with decreased vitamin D synthesis (143;150). The level of air pollution was negatively correlated to UVB irradiance at the ground surface in polluted areas, and positively associated with prevalence of low vitamin D status (150).

6.1.4. Sun avoidance (clothing, shade, sunscreen use). A number of skin cancer prevention campaigns have been launched during the last decades. "SunSmart" is one of the most famous programs that was designed to educate people about skin cancer and the ways it may be prevented (151;152). The five key recommendations for sun protection from SunSmart are: **slip** (cover as much of the body with cloths as possible), **slop** (reapply sunscreen with SPF >30 every 2 hours), **slap** (wear a broad-brimmed hat), **seek** (stay in the shade) and **slide** (wear wrap-around sunglasses) (151;152). Following all these recommendations may completely block vitamin D synthesis and result in vitamin D deficiency.

6.1.4.1. Clothing. The amount of vitamin D produced in the skin is proportional to the area of uncovered skin exposed to UVB radiation (1). Whole body exposure is practically possible only in tanning units or UV cabinets, since hardly more than 50 % of the body surface may be exposed to the sun at the same time (146). During the summer about 65-80% of the body surface usually remains covered with cloths (1;40;125). But not even 20-35 % of remained uncovered skin is directly exposed to the sun due to the geometry of the body (49;125). Thus, typical summer clothes may minimize vitamin D synthesis to 10-25 % of what is maximally possible.

6.1.4.2. Shade. When the influence of shade is taken into account, vitamin D production decreases further, especially in urban environments and nearby buildings (125). Thus, vitamin D deficiency is prevalent in urban areas (143;153;154). Shade reduces UVB fluence rates and vitamin D synthesis by approximately 60 % (155). It has been observed, that women who prefer to stay in the shade have 50% lower serum 25(OH)D concentrations (86 nmol/L) compared to women who prefer to stay in the sun (126 nmol/L) (142).

6.1.4.3. Use of sunscreens may seriously interfere with cutaneous vitamin D synthesis, leading to low vitamin D status (157). Sunscreens absorb mainly UVB, but also some UVA (157;158). Some studies have suggested that that use of sunscreen with sun protection factor (SPF) >8 may decrease vitamin D synthesis by 90%, and with SPF > 15 by approximately 95-99% (159-161). However, most recent studies showed little or no effect of sunscreens on vitamin D synthesis (158;162;163). The most likely reason for this is that in most cases sunscreens are not properly applied and the level of sun protecting is much lower than labeled SPF (158;163).

6.1.5. Skin pigmentation. The skin pigment melanin limits penetration of UVB radiation that results in low vitamin D synthesis in those persons (7). Individuals with skin type V and VI may need 5-10 times longer sun exposure than persons with skin type I and II in order to produce the same amount of vitamin D (108;164). Therefore, non-Caucasians

Figure 11. Vitamin D status according to skin type (Caucasians, skin type I-IV (156), non-Caucasians, skin type V-VI (114)).

usually have much lower vitamin D status than Caucasians, especially living at high latitudes (114). Blacks also have small seasonal variation of vitamin D (165).

However, a paradox has been observed by Glass et al. (156). In a study performed on Caucasian women with skin types I-IV, the lowest vitamin D status was observed in women with skin types I and II (**Figure 11**) (156). The same trend was observed by others (142). A possible explanation for this finding is that persons with light skin are generally recommended to avoid sun and to wear sunscreens whenever they are outdoors.

6.2. Vitamin D intake

Dietary intake is an important source of vitamin D during the winter (73). Vitamin D may be obtained from food that naturally contain vitamin D, dietary products fortified with vitamin D

and a variety of supplements (2;10). Since just few foods contain vitamin D in significant quantities, it might be very difficult to obtain adequate amounts of vitamin D only from food (56). Thus, supplementation may be needed during the part of the year when vitamin D cannot be produced in the skin.

6.2.1. "Recommended" intake does not mean "adequate" intake. The recommended vitamin D intake in most European countries, including Norway, is about 10 µg (400 IU) for children and 5-7.5 µg (200-300 IU) for adults (55). According to a report of the National Nutrition Council, the total vitamin D intake from both food and supplements in Norway is very close to the one that was recommended and is 10-12 µg for adults, similar (9-10 µg) for small children and 5-6 µg for adolescents (56). However, the prevalence of vitamin D deficiency is still high (73;120).

An intake of 400 IU may ensure that 97.5% of a population would maintain serum 25(OH)D levels > 25 nmol/L, but only 50 % of persons would maintain levels > 50nmol/L (166;167). According to recent observational and experimental studies the increment in serum 25(OH)D concentration after vitamin D supplementation is dependent the initial vitamin D status, and vary from 2.5 nmol/L per 100 IU of vitamin D intake in persons with low initial levels to 1.5 nmol/L or less for those with high serum 25(OH)D at baseline (9;78;88;168;169). Thus, supplementation with 400 IU/d may result in an increase of serum 25(OH)D by 6-10 nmol/L, 1,000 IU/d in an increase by 15-25 nmol/L, and a daily supplementation with 2,000 IU should be enough to raise 25(OH)D by approximately 30-50 nmol/L. This is in agreement with most published studies (9;43;78;88;166;168-172), except one by Holvik et al. that showed an increase of serum 25(OH)D concentrations by 34 nmol/L after only 1 month of vitamin D supplementation with 400 IU/d (173). That was enough to reach serum 25(OH)D >75 nmol/L (173). Other studies suggested that an intake of 1,500-3,000 (76;82;168;171;172;174;175) may be required to reach serum 25(OH)D > 75 nmol/L, and at least 1,000 IU/d may be needed to maintain vitamin D status at this level (166;167). Obese persons, persons with severe vitamin D deficiency and associated chronic diseases may require even higher doses of vitamin D supplementations (3,000-10,000 IU/d) (87;103;111;169;176).

The effect of oral vitamin D supplementation to increase serum 25(OH)D concentrations is also dependent on intestinal absorption of vitamin D. Thus, malabsorbtion syndrome as a consequence of chronic inflammatory diseases (Chron's disease, cystic fibrosis, short bowel syndrome) or pancreatic insufficiency may diminish effects of oral supplementation (126;177). In persons with decreased vitamin D absorption from the intestine single annual intramuscular injections of a "mega dose" of 600,000 IU may be preferred (178;179). This method of administration results in fast increase of serum 25(OH)D to the maximum values of 100-120 nmol/L during the first 6 months (178;179).

6.2.2. Vitamin D_3 or D_2? Vitamin D supplementation is available in two forms. The major preparation used in Norway is vitamin D_2 (AFI-D2 forte) (Table 2). Although vitamin D_2 and vitamin D_3 supplementation is regarded as equally potent and used to be administrated in the same doses, several studies have questioned their equivalency (5;180-183). A number of studies suggested that vitamin D_3 supplementation is 2-3-fold more effective to increase serum 25(OH)D concentrations than vitamin D_2 (180;183-185). Moreover, serum 25(OH)D levels seem to decay much faster after D_2 administration compared to D_3 administration (181). Relatively, the low potency of vitamin D2 supplementation was explained by diminished

binding of vitamin D_2 metabolites to BDP and short half-life (17;180). It is also possible that some methods used for serum 25(OH)D measurements may have underestimated the concentrations of vitamin D_2 metabolites due to low sensitivity (64;67;69;71). However, a recent study investigated the effect of vitamin D_2 and D_3 supplementation (1,000 IU/d for 11 weeks) on serum 25(OH)D increase using one of the most reliable methods (LC-MS), and concluded that vitamin D_2 and vitamin D_3 are equally potent to improve vitamin D status (5). Unfortunately, the study did not have a follow up to asses the decay of serum 25(OH)D concentrations after the end of the intervention. Similar 25(OH)D increases after administration of 1.25 mg D_2 or D_3 was also observed by Thacher et al. in a study performed on Nigerian children (182). Thus, further research might be needed to clarify possible differences in vitamin D_2 and D_3 bioavailability.

6.3. Excess body weight

During the last decades the prevalence of overweight (BMI 25-30 kg/m^2) and obesity (BMI > 30 kg/m^2) in Norway has followed the global trend and increased dramatically, reaching epidemic proportions (186;187). Just between 1990 and 2001 the prevalence of obesity increased from 4% to 11% for women and 5% to 13% for men (186). The average BMI in the adult Norwegian population has also increased significantly over these years and is above the upper limit of a normal BMI range (BMI 18.5-24.9 kg/m^2) (186;187). The increase of body weight is accompanied by increased risks of negative health outcomes and associated diseases (188). Vitamin D altered metabolism and vitamin D-related disorders are among these (132;176;189-198).

6.3.1. Serum 25(OH)D values decrease proportionally with increasing BMI (128;189;199). Thus, an increase of 1 kg/m^2 in BMI is associated with a decrease in serum 25(OH)D concentration by 0.7-1.3 nmol/L (128;189;199;200). Consequently, persons with normal weight have on the average about 20-25 nmol/L higher serum 25(OH)D concentrations than persons with BMI > 40 kg/m^2 (morbid obesity) (128;201). The prevalence of vitamin D deficiency in morbidly obese persons was reported to be 60-80%, that is 2-3-fold higher than in non-obese individuals, and 4-6-fold higher than in normal weight subjects (56;202-204). Obese persons commonly have low seasonal variation of serum 25(OH)D concentrations, and often do not reach the threshold of 75 nmol/L even during the summer (128;196). As a result of vitamin D deficiency sHPT is often observed in overweight and obese persons (191;200).

6.3.2. Serum 1,25(OH)$_2$D concentrations. Earlier studies reported elevated serum 1,25(OH)$_2$D values in subjects with high BMI related to high prevalence of sPTH (197;198;205;206). However, recent studies observed a negative correlation of serum 1,25(OH)$_2$D with BMI and adiposity, and a positive one with serum 25(OH)D (120;133;194;200;207). Thus, an increase of 1 kg/m^2 in BMI resulted in 0.8-0.9 pmol/l decrease of serum 1,25(OH)$_2$D concentrations (194;195). This supports the hypothesis that renal 1,25(OH)$_2$D synthesis is dependent not only on PTH levels, but also on substrate concentrations.

6.3.3. Influence of excess body weight on vitamin D status

6.3.3.1. Sequestration in fat tissue. Vitamin D is a fat-soluble compound, thus, it accumulates in the excess body fat and muscular tissue, and, therefore, has reduced bioavailability in overweight and obese individuals (190). As was calculated on the basis of an animal model (pigs), a woman of 70 kg with fat mass of 35 % (normal weight) would store almost three-quarters of the total vitamin D in the fat tissue, but 25(OH)D would be more equally distributed in the body: 35 % in fat, 30 % in serum, 20 % in muscles, and 15 % in all other tissues (208). Therefore, it is also likely that serum concentrations of vitamin D metabolites may be affected by a large overall volume of distribution (110).

6.3.3.2. Sun exposure habits. Other factors, such as sun exposure habits during the summer and diet composition, may also contribute to low vitamin D status in persons with excess body weight (194;196;209;210). Obese persons have reduced outdoor activity during the summer, and generally prefer to cover as much of the body with cloths as possible (196;209). Although they have a large skin surface and possible may produce more vitamin D than normal weight persons, the same sun exposure results in almost 60 % less increase in serum 25(OH)D concentrations in obese than in non-obese (190). The mechanism behind it is not fully understood, but it has been proposed that obese may have altered release of vitamin D produced in the skin into blood circulation, since subcutaneous fat may sequester more vitamin D. Supporting this hypothesis, vitamin D_3 concentrations in subcutaneous fat tissue and serum were positively correlated in a pilot study on obese adults undergoing gastric bypass surgery (211).

6.3.3.3. Inadequate vitamin D consumption. Obese persons seem to benefit less from the same dose of oral vitamin D supplementation than non-obese persons (190;212). At the same time, they have generally decreased vitamin D intake compared with normal weight persons (210). A number of studies have investigated the effect of different doses of vitamin D supplementation in persons with excess body weight (127;176;190;212;213). The general conclusion is that the efficiency of vitamin D supplementation to increase serum 25(OH)D concentrations is dependent on BMI, and that higher doses of supplementation are required in obese persons than in normal weight subjects to reach and maintain optimal vitamin D status (212;213). In a study of Zittermann et al. vitamin D_3 supplementation with 3,300 IU/d for 1 year in patients with BMI > 27 kg/m^2 resulted in an increase of serum 25(OH)D by 56 nml/L, and was efficient in giving 25(OH)D concentrations > 80 nmol/L (176). For persons with BMI > 40 kg/m^2 a supplementation with 40,000 IU per week may be necessary in order to reach serum 25(OH)D >80 nmol/L (127).

6.3.4. Does vitamin D deficiency cause obesity?

Adipocytes express both VDR and 1ά-hydroxylase and may convert 25(OH)D to 1,25(OH)$_2$D (214;215). Experimental studies on adipose tissue cell lines confirmed the importance of 1,25(OH)$_2$D in modulating adipocyte function by regulating apoptosis, adipose tissue fat depot location and glucorticoid production (215;216). Observational studies have also reported that serum 25(OH)D concentrations were associated with a number of metabolic risk factors (199;217-223). Thus, vitamin D status was positively related to insulin sensitivity and negatively to fasting glucose, insulin levels, adiponectin concentrations and other markers of diabetes II type (waist circumference,

haemoglogin A_{1c}) (199;217-223). Serum 25(OH)D concentrations were also associated with changes in lipid profile (220;221;223). Moreover, vitamin D intake with food and supplements was an independent predictor of obesity in the study performed by Kamycheva et al. (210).

Based on these findings, it has been proposed that vitamin D deficiency may play a role in development of common obesity (127;176;224;225). Several studies were initiated to test this hypothesis, and to investigate if improvement of vitamin D status may result in weight loss (127;176;224). RCT revealed no effect of vitamin D supplementation on weight loss (127;176). On the other hand, weight loss was associated with improvement of vitamin D status (226). Thus, vitamin D deficiency seems to be a consequence of obesity, but not the other way around. However, vitamin D supplementation in obese persons may enhance the beneficial effects of weight-reduction programs, and may possibly improve metabolic, cardiovascular and mental health in these persons (103;176;226).

6.4. Genetic variation and vitamin D status

According to GWAS with about 34,000 persons from 15 European cohorts, the risk of vitamin D deficiency and insufficiency may be genetically determined (13). The genetic variations in three loci were identified to be associated with serum 25(OH)D levels (13;227). Among them are: 1) the locus of the gene coding the enzyme involved in cholesterol synthesis from 7-DHC (7-DHC-reductase), 2) CYP2R1, the gene that encodes the enzyme involved in the hydroxylation of vitamin D to 25(OH)D in the liver, and 3) GC that encodes DBP (13;227). The most unlucky combination of the genetic variants (all three loci associated with low vitamin D status) was associated with a 2.5-fold higher risk of serum 25(OH)D < 75 nmol/L than the most lucky combination (none of the loci associated with low vitamin D status) (13). Moreover, genetic factors seem to explain about 50% of serum 25(OH)D variability during the summer, although, environmental factors may play a major role during the winter (21). Thus, testing gene polymorphism of the vitamin D associated loci may be useful to identify persons with high risk of vitamin D deficiency.

6.5. Who is at risk for Vitamin D deficiency?

There are several groups of people that are at high risk for vitamin D deficiency including infants, adolescents, elderly, vegetarians, non-Caucasians living at northern latitudes, skin type I and II individuals avoiding sun, overweight and obese, persons with malabsorbtion, and individuals using medications that may interfere with vitamin D endocrine system, such as anticonvulsants, rifampicin, cholestyramine, highly active antiretroviral treatment and glucocorticoids (61;72;76;228).

Vitamin D deficiency should be checked for in children with symptoms common for rickets (pain, irritability, bone deformations, impaired growth) and often infections, as well as in adults with evidence of poor bone health (osteomalacia, osteopenia, low BMD, osteoporosis, fractures), chronic pain, proximal muscle weakness and fatigue (72;76;228). Recently it has been suggested that patients with depression, autoimmune diseases, diabetes, heart diseases, hypertension and cancer may also have vitamin D deficiency or VDDS (76;107).

7. VITAMIN D AND CANCER

The role of vitamin D and its derivatives in cancer prevention and progression has been the topic of numerous recent investigations. It is evident that vitamin D may affect cancer risk and mortality, by action directly on cancer cells and by modulating anti-cancer immune responses (17;83;88). 1,25(OH)$_2$D modulates a wide array of molecular reactions that result in anti-proleferative, pro-differentiating, anti-inflammatory, anti-metastatic, pro-apoptotic, and immunomodulatory effects (229;230). Colorectal (CRC), breast (BCa), and prostate cancers (PCa) are among the most studied malignancies in regard to vitamin D actions.

7.1. Mechanisms of anti-cancer effects

Most of cancer cells express VDR that mediates both genomic and non-genomic effects of vitamin D. CRC, BCa, and PCa cells also express 1ά-hydroxylase and may convert 25(OH)D to 1,25(OH)$_2$D (16;231), and 24-hydroxylase that is responsible for vitamin D utilization and converts both 25(OH)D and 1,25(OH)$_2$D to their less-active metabolites (17). The balance between these enzymes may be important for cancer development and prognosis. This also suggests that vitamin D supplementation and 24-hydroxylase-resistent analogs may possibly be used in cancer prevention and therapy (229). However, during cancer progression tumor cells often decrease expression of 1ά-hydroxylase and have reduced responds to VDR activation (232-234). At the same time, high expression of 24-hydroxylase was observed in cancer cells (232;233).

7.1.1. Regulation of cell growth, proliferation, differentiation and apoptosis. Inhibition of cancer cell growth by 1,25(OH)2D most probably occurs due to cell cycle arrest and stimulation of apoptosis (230). In PCa cells 1,25(OH)$_2$D treatment results in cell cycle arrest in G$_1$/G$_0$ phase, inhibition of cell proliferation, and decreased expression of the *c-myc* oncogene (235-237). In BCa cells 1,25(OH)$_2$D facilitates apoptosis as well as expression of several key proteins involved in cell proliferation and differentiation (238;239). Both in vitro and in vivo studies show that 1,25(OH)$_2$D has pronounced anti-proliferative and pro-differentiation effects on CRC (240;241).

7.1.2. Regulation of androgen and estrogen receptor signaling. Growth of PCa and BCa cells is dependent on activation of androgen and estrogen receptor signaling pathways. 1,25(OH)$_2$D seems to be involved in regulation of both sex-steroid receptors (229). Thus, in BCa cells 1,25(OH)$_2$D inhibits expression of estrogen receptors and decreases estrogen-mediated cell proliferation (242). In PCa cells 1,25(OH)$_2$D in general inhibits expression of androgen receptors, but in androgen-independent cell lines 1,25(OH)$_2$D up-regulates expression of androgen receptors, and facilitates androgen-dependent anti-ptoliferative affects (236;243).

7.1.3. Anti-inflammatory actions. In cancer cell lines, including PCa, BCa, CRC, 1,25(OH)$_2$D treatment gives anti-inflammatory effects like inhibition of prostaglandins synthesis, modulation of cycloxygenese-2, 15-hydroxyprostaglandin dehydrogenase, prostaglandin receptors and prostagalngin pathway genes; inhibition of stress-activated kinase signaling and induction of MAP kinase phosphatase 5; inhibition of nuclear factor κB activation and signaling; regulation of inflammatory cytokines production (229).

7.1.4. Inhibition of angiogenesis. In vivo and in vitro studies on BCa revealed that $1,25(OH)_2D$ inhibits expression of vascular endothelial growth factor (VEGF), the most active stimulator of angiogenesis, and decreases tumor visualization in mice (244). VEGF and matrix metallopeptidase-9 were also suppressed after $1,25(OH)_2D$ treatment in a number of PCa cell lines (244;245). Moreover, tumors from VDR knockout mice had increased expression of VEGF, platelet-derived growth factor, and hypoxia-inducible transcription factor-1ά (246). $1,25(OH)_2D$ was also shown to inhibit directly proliferation of endothelial cells (245;246).

7.2. Observational studies

A large amount of epidemiological data on the association of vitamin D status and cancer risk and mortality come from ecological studies that used surrogate measures of vitamin D status, such as UVB fluence rates, latitude, season, skin cancer incidence and dietary vitamin D intake (132;139;247-256). Grant conducted a multifactorial ecological study of cancer mortality rates in the United States using UVB fluence rates in July as a surrogate measure of the vitamin D status, and found nearly the same associations of "vitamin D status" with breast, colon, rectal, oesophageal, renal, stomach, gallbladder, pancreas, prostate cancers as well as with multiple myeloma and non-Hodgkin's lymphoma (249), even thought these cancers have different contributing risk factors.

Ecological studies have been accompanied by a large number of cohort, case-control, and cross-sectional studies aimed to shed light on the direct association between vitamin D and cancer. Most attention was concentrated around common cancer types such as CRC, BCa, and PCa. Due to a large number of studies and the discrepancy between them it seems more reliable to draw conclusions from meta-analysis of the observational studies recently performed.

7.2.1. Colorectal cancer (CRC). According to meta-analysis by Gandini et al., there is a consistent inverse correlation between serum 25(OH)D concentrations and risk for colorectal cancer (257). Based on 9 studies that included 2,630 cases, the summary RR for colorectal cancer was 0.85 (CI, 0.79-0.91) for 25 nmol/L. This is in agreement with earlier published mata-analysis by Yin et al., that reported the summary OR for colon cancer 0.78 (CI, 0.54-1.13), rectal cancer 0.41 (CI, 0.11-1.49), and for types both of cancers 0.57 (CI, 0.43-0.76) for 50 nmol/L increase (89). Moreover, serum 25(OH)D concentrations at diagnosis and vitamin D intake were inversely correlated with colorectal cancer mortality (258;259).

7.2.2. Breast cancer (BCa). In a meta-analysis by Yin et al. based on 9 publications, the RR of BCa for an increase of serum 25(OH)D by 50 nmol/L was 0.73 (CL, 0.60-0.88) (260). The reported association was weaker than earlier suggested (91). Garland et al. suggested similar associations between vitamin D status, breast and colorectal cancer (91). Thus, an increase of serum 25(OH)D concentrations from < 40 nmol/L to > 95 nmol/L was associated with 55-58 % reduction in risk for both cancer types. Gandini et al. found no association between vitamin D status and BCa (RR 0.89 (CI, 0.81-0.98) for 25 nmol/L) in the pooled analysis of 10 studies (257).

7.2.3. Prostate cancer (PCa). No association between vitamin D status and PCa risk was found in two recent meta-analysis (257;261). The summary RR was 0.99 (CI, 0.95-1.03) for 25 nmol/L in the meta-analysis performed by Gandini et al. (257), and OR was 1.03 (CI, 0.96-

1.11) for 25 nmol/L in the study by Yin et al. (261). One study that was included in both meta-analyses reported a U-shape in the association between PCa risk and serum 25(OH)D concentration (262). Thus, the risk was highest for men with serum 25(OH)D values < 19 nmol/L and > 80 nmol/L, and the lowest risk was reported for men with serum 25(OH)D concentrations within the range of 40-60 nmol/L. However, this finding is likely to be just an isolated observation, since the upper quartiles of 25(OH)D concentrations were the same as in other studies showing protective or no effect (257). Another meta-analysis has estimated the role of SNP of VDR in PCa risk based on 36 recent studies (263). The authors concluded that the *Apal a* allele was associated with decreased risk of PCa among Asians, and the *Fokl f* allele was weakly associated increase risk of PCa in Caucasians (263). Improved PCa survival was observed for persons with pre-diagnostic serum 25(OH)D concentrations > 80 nmol/L (264).

7.3. Clinical trials

7.3.1. Vitamin D for cancer prevention. Clinical studies on cancer prevention have been conducted to investigate the effects of vitamin D supplementation on CRC and BCa risk (100;240;265). Since cancer cells and cells within the tumor microenvironment may convert 25(OH)D to $1,25(OH)_2D$, is it believed the increase of serum 25(OH)D concentrations after adequate vitamin D supplementation may result in local $1,25(OH)_2D$ synthesis and thereby anti-proliferative effects. Additionally, 25(OH)D may also activate VDR.

The Women Health Initiative (WHI) study investigated the effect of supplementation with 400 IU/d of vitamin D_3 primarily to prevent fractures, but the secondary outcomes of the study were risks for BCa and CRC (266). Initial analysis revealed no association between vitamin D supplementation and cancer risk (267). However, the reanalysis of the data suggested that the effect of vitamin D on CRC risk may be modified by hormone-replacement therapy (265). Thus, protective effects of vitamin D against CRC were shown only for women who had no estrogen treatment during vitamin D intervention.

A small pilot RCT in 92 men and women with a history of pathology-confirmed colorectal adenoma reported that vitamin D3 supplementation with 800 IU/d for 6 months resulted in increased differentiation of normal colorectal epithelial cells and normalization of the colorectal crypt proliferative zone (240). Thus, the study supported the role of vitamin D in CRC development.

A large, placebo controlled, double-blind, 4-year longitudinal clinical trial in postmenopausal women with 1,100 IU/d vitamin D_3 supplementation and/or calcium (1400-1500 mg) reported 77 % decreased risk of getting any type of cancer in vitamin D+calcium arm compared with placebo arm (RR 0.23 CI, 0.09-0.60; P < 0.005) (100).

7.3.2. Vitamin D for cancer treatment. Most anti-cancer clinical trials with vitamin D were conducted on PCa patients and used $1,25(OH)_2D$ (268). Some studies also investigated the effectiveness of vitamin D supplementation and vitamin D analogues.

7.3.2.1. Vitamin D3 supplementation. A small pilot study in 15 PCa patients reported that supplementation with 2,000 IU vitamin D_3 for 21 months prolonged the doubling time of prostate-specific antigen (PSA), an important marker of tumor growth (269).

A recent Phase II study in metastatic BCa patients revealed no effects of vitamin D_3 supplementation in dose of 10,000 IU/d for 4 months on palliative outcomes or prognosis of advanced BCa (111).

7.3.2.2. 1,25-dihydroxyvitamin D. Administration of $1,25(OH)_2D$ alone or in combination with standard cancer therapy was reported in clinical trials on PCa. Although, some regimens of $1,25(OH)_2D$ treatment may result in hypercalcemia, the intermittent administration with high doses given 3 times a week or once a week was shown to be safe and resulted only in transient hypercalcemia and rare renal stones (270;271). The effect of the treatment was often evaluated based on serum PSA levels and overall survival (270). $1,25(OH)_2D$ was in most cases used in combination with dexamathasone, paclitaxel, or carboplatin (272).

High-dose oral $1,25(OH)_2D$ administration together with dexamethasone and carboplastin, or dexamethasone alone in PCa patients resulted in significant PSA decrease (two Phase II trials) (271;273). However, these results were not confirmed by ASCENT I clinical trial conducted in advanced PCa patients that observed almost no effect of $1,25(OH)_2D$ on PSA concentrations (274). $1,25(OH)_2D$ was administrated in formulation of DN-101 (Novacea) orally once a week together with taxotere and resulted in significant improvement of overall survival. Based on inspiring results of ASCENT I, a large Phase III (ASCENT II) was initiated (275). ASCENT II had two arms: 1. docetaxel (new regimen, once every 3 weeks) as a control arm, and 2. docetaxel (old regimen, once a week) + DN-101. Unfortunately, this study was stopped due to excess mortality in the study arm. At first, it was explained by possible $1,25(OH)_2D$ toxicity, but further analysis of the results suggested that the excess mortality was caused by asymmetric study design and less effective docetaxel regimen in the study arm (275).

7.3.2.3. Vitamin D analogs. Development of less hypercalcemic analogs of $1,25(OH)_2D$ may solve the problem of administration of active vitamin D metabolites in high enough doses to cause therapeutic effects. Recently several $1,25(OH)_2D$ analogues became available including EB1089 (seocalcitol), 1-ά-vitamin D_2, inecalcitol, and paricalcitol (229;276).

Conclusion. Although the epidemiological data firmly show an association between serum 25(OH)D concentrations, vitamin D intake, and solar radiation, the lack of well designed Phase II and Phase III RCT makes it difficult to define a biologically optimal dose and TUL for vitamin D intake. At this moment there are over 300 open intervention studies that have been initiated to investigate the effect of vitamin D on cancer incidence and mortality (277). Thus, in the nearest future we will hopefully have answers to many of our questions.

8. GENERAL METODOLOGICAL CONSIDERATIONS

8.1. Analysis data base

Data on overweight and obese persons were provided by a Metabolic and Medical Lifestyle Management Clinic in Oslo, Norway, collected from September 2001 to January 2007. It contained data on serum 25(OH)D and 1,25(OH)$_2$D concentrations, body composition parameters (BMI, body weight, fat mass, adiposity), season of blood sampling, gender, age and primary diagnosis in 1779 adults (1464 women and 315 men) and 102 children (70 girls and 32 boys). Data on co-morbidities were also recorded in the database (Paper 2 and 3).

8.2. Volunteers

To avoid any contribution from solar radiation, intervention studies were conducted during the winter months (November to March), a time of the year when no vitamin D is synthesized in skin by sun exposure at our latitudes.

A total of 54 healthy volunteers (15 men and 39 women), aged between 21 and 65 years, were included in the interventional studies (Paper 4 and 5). All volunteers were living in Oslo (59°N). Almost all participants (>90 %) were Caucasians and had Fitzpatrick skin types II or III. The participants were asked to fill out questionnaires that screened for: age, weigh, height, skin type, sun exposure, indoor tanning habits, and food.

Exclusion criteria were: presence of severe disorders and medical conditions known to effect vitamin D status; pregnancy or plans to become pregnant; high-dose vitamin D supplementation, winter vacations to southern latitudes and indoor tanning late than 8 weeks before initiation of the study or plans for traveling to southern latitudes during the study.

8.3. Serum 25(OH)D and 1,25(OH)$_2$D assays

❖ *Serum 25(OH)D and 1,25(OH)$_2$D in overweight and obese persons* were analyzed at the Hormone Laboratory, Aker University Hospital and Fürst Laboratories, but by radioimmunoassays (RIA) (DiaSorin, Stillwater, MN, USA). Vitamin D deficiency was defined as serum 25(OH)D < 50nmol/L and vitamin D sufficiency as concentrations ≥ 75 nmol/L (Paper 1, 2, and 3).

❖ *Serum 25(OH)D of 54 volunteers, participated in intervention studies,* were analyzed at the Haukeland University Hospital, Bergen, Norway. The 25(OH)D assay was performed by LC-MS method (LC∕MSD SL; Agilent Technology, CA). The mean recovery of calcidiol was 77.2% (SD 3.9%) and the interassay variation was 4.9%, with a detection limit < 4 nmol/l (Paper 4 and 5).

8.4. Body composition and BMI

Body composition parameters and BMI were estimated using bioelectric impedance analysis (BIA) with Tanita Body Fat Monitors, TBF 300 GS (Tanita Corp of America, USA) (Paper 2 and 3). Overweight in adults was defined as a BMI in the range 25 – 29.9 kg/m^2. Obesity and morbid obesity were defined as a BMI ≥ 30 kg/m^2 and ≥ 40 kg/m^2, respectively. In children and adolescents obesity and overweight categories were defined based on specific centile curves standardized for age and sex (Paper 3). Overweight was defined as a BMI between the 85th and 95th percentiles. Obesity was defined as a BMI ≥ 95th percentile.

8.5. Vitamin D intake

Vitamin D intake of volunteers that participated in the intervention studies was analyzed based on food frequency questionnaires (Paper 4 and 5). No vitamin D intake or supplementation data were recorded in the database on overweight and obese persons (Paper 2 and 3). RDD of D_3 has been increased in 2004 from 5 µg/d to 7.5 µg/d. D_2 supplementation for adults was not available in Norway during the observation period.

8.6. UV exposure

❖ ***Sources of UV radiation were*** commercially available and approved type 3 tanning units equipped with Solarium Super Plus 100 W tubes (2.0 % $UVB_{280\text{-}320\ nm}$, device S_2) (Paper 4), or with Golden Sun RS 100 W and Beauty Sun S 25 W spaghetti tubes (Wolff System, Basel, Switzerland) (2,15% $UVB_{280\text{-}320\ nm}$, device S_3) (Paper 5). The spectral distributions of the lamps were provided by the producer (**Figure 12**). Additionally, fluence rates of both tanning units were measured using a UV-meter (Solar Light Company Inc.) (paper 4 and 5). Emission spectra of S_3 and of the sun (Oslo, 22 July 2010, 12.00 AM) were measured with a AvaSpec ULS fiber optic spectrometer using AvaSoft 7.3.1 (Avantes BV, NL-6961 RB Eerbeek, Netherlands) (Paper 5).

❖ ***Efficiency spectra of vitamin D formation*** were calculated based on action spectra of previtamin D_3 synthesis in the human skin (CIE-2006) (278). CIE erythema weighted UV doses are presented as Standard Erythema Dose (SED; 1 SED = 100 J/m^2). One SED is equivalent to about 0.5 MED for the most sensitive type 1 skin (1 MED = 200 J/m^2) (Paper 4 and 5).

8.7. Data analysis

❖ ***In obese and overweight persons correlations*** between 25(OH)D, 1,25(OH)$_2$D, BMI, adiposity, age were analyzed using SigmaPlot 10.0 and SPSS 15.00 for Windows (Paper 2 and 3). The monthly data of the variables were presented as means ± SEM. Correlation analysis was also performed for 25(OH)D quartiles using one-way ANOVA and the Bonferroni correction. The alpha criterion for two-tailed statistical significance was defined < 0.05.

❖ ***Data for healthy volunteers*** were analyzed using Sigma Plot 10.0 for Windows. The variables are presented as means ± SEM. The criterion for statistical significance is defined as $P < 0.05$. (Paper 4 and 5)
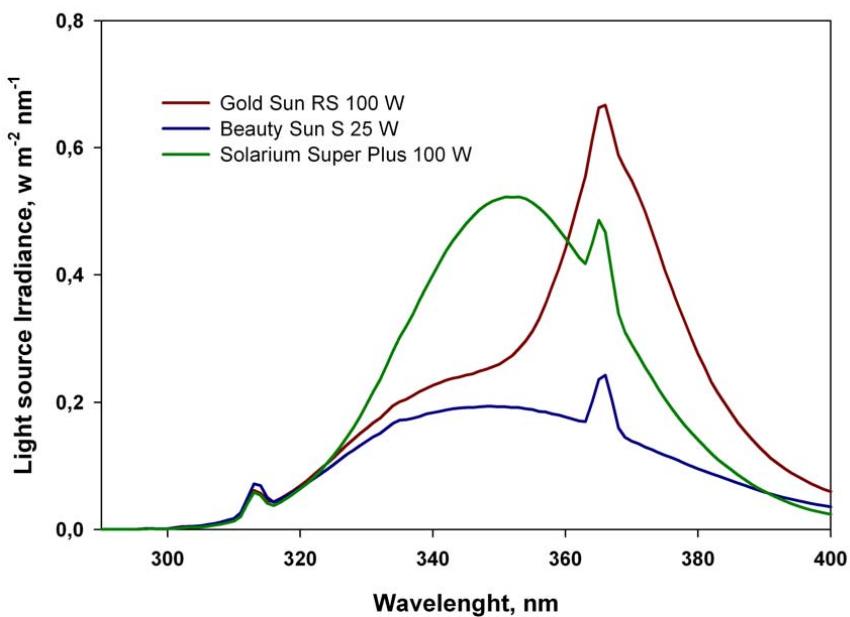
9. SUMMARY OF PUBLICATIONS

Paper 1

Obesity and increased risk of cancer: Does decrease of serum 25-hydroxyvitamin D level with increasing body mass index explain some of the association?

Aims: Our earlier investigations suggest that serum 25(OH)D levels decrease with increasing BMI. At the same time, excess body weight is associated with increased risk of cancer. Thus, we wanted to evaluate the possible connection between cancer risk, BMI and vitamin D status.

Methods: In this study, we analyze data published in current meta-analysis, prospective studies, and systematic reviews on cancer-specific risk attributed to high BMI and low vitamin D status.

Results: Our study suggests that a low vitamin D status may explain at least 20% of the cancer risk attributable to high BMI. The contribution of low 25(OH)D to the increased cancer risk with increasing BMI may be different for different cancer types. Thus, we find 40% for breast cancer, and 26 and 75% for colorectal cancer in men and women, respectively.

Paper 2

The serum 25-hydroxyvitamin D is a predictor of 1,25-dihydroxyvitamin D in overweight and obese patients.

Aims: Although, it is generally accepted that serum $1,25(OH)_2D$ concentrations remain almost constant in time, some groups of patients may have decreased $1,25(OH)_2D$ concentrations. We aimed to investigated the factors that may directly influence serum $1,25(OH)_2D$ concentrations.

Methods: In the present study the associations between 25(OH)D, $1,25(OH)_2D$, BMI, body weight, fat mass, adiposity, season, gender and age were analyzed in 1779 obese and overweight patients.

Results: Serum 25(OH)D among the other studied factors was the strongest predictor for serum $1,25(OH)_2D$. The $1,25(OH)_2D$ concentrations were 25.4 pmol/L (Cl, 19.3-31.5) lower in the lowest 25(OH)D quartile to compared with highest quartile. A seasonal variation was observed for both vitamin D metabolites. Among all body composition parameters, adiposity had the strongest predictive power on serum $1,25(OH)_2D$ concentrations. Serum $1,25(OH)_2D$ concentrations were also associated with age.

Paper 3

Vitamin D status in Norwegian children and adolescents with excess body weight.

Aims: The purpose of this study was to determine the prevalence of vitamin D deficiency and insufficiency in Norwegian children and adolescents with excess body weight.

Methods: Vitamin D status and seasonal variations of 25(OH)D and 1,25(OH)2D were analyzed in 102 children and adolescents (70 girls and 32 boys), 8–19 yr of age, with overweight and obesity.

Results: Overall, 50% of the children and adolescents included in the study had vitamin D insufficiency and 19% had vitamin D deficiency. Only 42% of teenagers had 25(OH)D levels ≥75 nmol/L vs. 72% of preteens. Serum 25(OH)D concentrations had a typical seasonal variation with the highest values observed during the summer. In contrast, serum $1,25(OH)_2D$ had a peak during the spring.

Paper 4

Sunbeds as vitamin D sources.

Aims: We wanted to determine whether repeated exposures to small UV doses from a commercial sun bed are efficient to increased serum 25(OH)D concentrations. We also aimed to investigate the impact of initial vitamin D status on serum 25(OH)D increase.
Methods: Healthy volunteers were randomly divided into two groups that had different tanning regimens: 6.75 MED and 13.5 MED (Sun_2 device).
Results: The mean 25(OH)D values after exposure were ~80 nmol/L and the mean increase (~15 nmol/L) was the same for all UV doses given. Persons with the lowest initial levels got the largest increase. The level in this group was back to the pre-exposure level after 2–4 weeks.

Paper 5

Effect of vitamin D supplementation and ultraviolet B exposure on serum 25-hydroxyvitamin D concentrations in healthy volunteers.

Aims: The aim of the present study was to compare the efficiency of oral vitamin D supplementation and multiple UVB exposures for improvement of the vitamin D status.
Methods: Healthy volunteers were randomly divided into two groups. Group 1 started with vitamin D supplementation (2,000 IU/d for 30 days) and continued with 10 Sun_3 exposures. Group 2 started with 10 Sun_3 exposures and continued with vitamin d supplementation.
Results: Oral supplementation with vitamin D_3 was slightly more beneficial than UV exposure (10 Sun_3 exposures of total dose 23.8 SED; vitamin D weighted dose: 134 J/m^2 per 1 SED). The first phase of intervention resulted in an increase of serum 25(OH)D concentrations by ~25 nmol/L. The total serum 25(OH)D increase after both interventions in both groups was 31.3 nmol/L (SEM ± 3.8 nmol/L; P<0.001). At the end of the study 61% of the volunteers had serum 25(OH)D ≥ 75 nmol/L. The results of our study indicate that daily whole body sun exposure at ~0.5 SED may be enough to achieve and maintain serum 25(OH)D concentrations ≥ 75 nmol/L, if the initial serum 25(OH)D concentrations are ≥ 50 nmol/L. This dose almost equals to 2000 IU/d of oral vitamin D supplementation, and about 2 hours per week of sun exposure to 1/3 skin surface area at Oslo latitude around midday during the summer.

10. DISCUSSION

10.1. Vitamin D and artificial UVB sources

Sun is the most efficient natural source of vitamin D. Thus, sun exposure during the summer may provide essential amounts of vitamin D_3, some of which is stored for the coming winter (61). The serum 25(OH)D levels > 80 nmol/L at the end of the summer are considered necessary to avoid vitamin D deficiency (25(OH)D < 50 nmol/L) during the winter (140). However, it is not clear how much sun exposure is needed for optimal vitamin D synthesis (125). According to Holick's rule, exposure of ¼ body skin surface to the sun for ¼ MED (~0.5-0.8 SED) is required to produce enough vitamin D, and is equal to 1,000 IU/d oral vitamin D (33). Recent studies examining serum 25(OH)D concentrations at the end of the summer or after controlled UVB exposure do not support this advice (125). It seems that longer sun exposures may be needed to reach an optimal vitamin D status, and the recommended exposure is probably enough just to prevent vitamin D deficiency during the summer (40;140). For people living in urban areas even the current advice seems to be difficult to follow. It is not always possible for them to incorporate "sunshine minutes" into daily working schedule, since the best exposure time is the midday (44;46). Thus, vitamin D deficiency is prevalent even in the sunny countries (115;279).

10.1.1. How much vitamin D do we get from the sun? At northern latitudes vitamin D synthesis takes place only during the summer months (April-October). Therefore, serum 25(OH)D concentrations vary during the year, usually in the range of 50-80 nmol/L, with a peak in July-September, and a nadir in February-March . Sun exposure habits during the summer may contribute significantly to seasonal variation of vitamin D. The time spend outdoors during the summer and the area of uncovered skin surface exposed to the sun correlate positively with serum 25(OH)D concentrations (142;145).

Thieden et al. (138) estimated vitamin D status and summer sun exposure behavior in Danish indoor and outdoor (gardeners) workers, and found that serum 25(OH)D concentrations were associated with the cumulative UVR dose obtained during the summer (mean: 156 SED), daily time spend outdoors (mean: 1.4 SED), number of days with large body surface exposed to the sun (upper body) (mean: 24 days), and constitutive pigmentation. (**Table 5. Part I**). Sun exposure for 1.4 SED/d (~16 minutes for Oslo) during the summer is enough to reach the 25(OH)D levels > 80nmol/L at the end of the summer, and to maintain serum 25(OH)D > 50 nmol/L during the winter.

This is in agreement with a recent study (140) that estimated sun exposure behavior and seasonal variation of vitamin D in a UK population. During spring and summer the average daily sun exposure was ~0.5 SED (6 minutes for Oslo), which is close to that suggested by Holick as an optimal exposure for vitamin D synthesis. This dose was not enough to reach the threshold for vitamin D sufficiency (25(OH)D ≥ 75 nmol/L) at the end of the summer (140).

Burgaz. et al. observed a large difference between serum 25(OH)D concentrations in two groups of women with different sun exposure habits. Women who during the summer preferred to stay in the sun instead of in shade, had skin type III or IV, and of normal weight, had 64 nmol/L higher serum 25(OH)D concentrations than women that preferred shade, had skin type I or II, and were obese (142) (**Table 5. Part I**). The results of the study also suggested that the 25(OH)D levels > 100 nmol/L at the end of the summer may maintain serum 25(OH)D > 75 nmol/L throughout the year (142). Vacations to sunny countries were also

associated with increased serum 25(OH)D concentrations. A woman who had 3 vacations to a sunny country during the winter had serum 25(OH)D levels of 139 nmol/L. A large increase in serum 25(OH)D concentrations (47 nmol/L) was observed in patients with psoriasis that received climate therapy in Gran Canaria (146;280). After a whole body sun exposure to a total dose of 166 SED over 15 days serum 25(OH)D values increased from 57 nmol/L to 105 nmol/L (**Table 5. Part I**). Another study by Vähävihu et al. (281) reported an increase in serum 25(OH)D concentrations by 13.4 nmol/L (total dose 60 SED) and 24 nmol/L (total dose109 SED) after 2 weeks-climate therapy in Gran Canaria in patients with atopic dermatitis (281).

Table 6. "Rule of nines" (145).

Body area	Skin surface, %
Head	9
Both arms	18
Both legs	36
Trunk	36

Persons working outdoors also seem to have a much better vitamin D status than indoor workers (144). Thus, in the study by Barger-Lux outdoor workers (landscaping, construction work, farming, and recreation) had serum 25(OH)D concentrations of 122 nmol/L (100-154 nmol/L), which decreased to 74 nmol/L during the winter (145). The average time they spent outdoors was 38 hours per week (**Table 5. Part I**). The vitamin D status was dependent on the area of body skin surface that was uncovered during sun exposure. The skin area was calculated based on "Rule of nines" (**Table 6**).

10.1.2. Do UVA-tanning units contain enough UVB for vitamin D synthesis? Even though modern tanning units are often called "UVA-sun beds" it does not mean they emit no UVB, but that they emit a lot of UVA. In fact, the tanning units allowed in Norway (CIE erythema weighted UV to 0.3 W/m^2: 0.15 W/m^2 of UVB and 0.15 W/m^2 of UVA) emit slightly more UVB than sun at Oslo latitude during the summer (282). Thus, tanning devices may be useful to study the effects of solar UV exposure since it can be simulated under well controlled conditions. Our group has studied the efficiency of UVB radiation to provoke vitamin D synthesis using three different tanning units in regard to UVB emmission and intensity (43;52;283). In our first study (283) we used lamps (Life Sun S 100W (device Sun$_1$)) with the highest UVB content (UVB$_{280-320 nm}$ 3,9%). The two following studies were performed with lamps with almost 2-fold lower UVB content (device Sun$_2$) (Paper 4), (device Sun$_3$) (Paper 5). All studies were performed between October and April, a time of the year when vitamin D synthesis from the sun exposure does not occur.

In general, the serum 25(OH)D increase was highest after exposure to a tanning unit with high UVB content (52;283). After 10 whole body exposures to S$_1$ (total dose of 8.5 MED over 4 weeks) serum 25(OH)D concentrations increased on the average by 26 nmol/L, from initial levels of 65 nmol/L to 92 nmol/L (**Table 5. Part II**). After exposure to Sun$_2$ and Sun$_3$ the increase in serum 25(OH)D concentrations was lower than for Sun$_1$, but Δ25(OH)D and final vitamin D status were dependent on initial serum 25(OH)D concentrations (Paper 4). The mean increase after exposure to Sun$_2$ was 15 nmol/L disregard of UV dose (6.75 MED or 13.5 MED over 7 weeks).

Further, we aimed to compare the efficiency of oral vitamin D supplementation (2,000 IU/d for 4 weeks) and 10 exposures to S$_3$ (total dose of 23.8 SED (9 MED), to increase and

maintain serum 25(OH)D concentrations (Paper 5). Volunteers were randomized into two groups: Group 1 and Group 2. Group 1 received vitamin D supplementation at first and then continued with 10 whole body exposures. Group 2 started with 10 exposures and than continued with vitamin D supplementation. As in a previous study, serum 25(OH) increase was dependent on initial values. Thus, volunteers that did not have vitamin D deficiency after both interventions reached average concentrations of > 90 nmol/L. Vitamin D deficient participants also significantly increased serum 25(OH)D concentrations, although they did not reach the threshold of vitamin D sufficiency (**Table 5. Part II**). Vitamin D supplementation with 2,000 IU/d had almost the same effect on vitamin D status as 10 whole body exposures. The increase of serum 25(OH)D after first intervention was 25 nmol/L, and after both interventions 31 nmol/L on average.

The UV dose given in the study was equal to ~0.5 SED/d sun exposure to the whole body, or almost 1 MED to ¼ of body surface at Oslo latitude, that is about a 4-fold higher dose than previously recommended (33). Thus, our studies indicate that the recommended sun exposure is unlikely to be adequate for optimal vitamin D synthesis. Our findings are in agreement with other studies on the indoor tanning devices (**Table 5. Part II**). Rhodes el al. simulated the summer sun exposure by using a tanning device equipped with Arimed B and Cleo Natural lamps (5 % UVB). An exposure equal to 3.3 SED of solar UV dose (39 minutes in Manchester sun, UK) (36 minutes in Oslo sun) was given to 35 % of body surface (skin area that is usually stays uncovered during the summer) (40). After 18 exposures of a total dose of 20 SED serum 25(OH)D concentrations increased significantly, but just to reach values > 50 nmol/L. Only 26 % of participants had serum 25(OH)D > 75 nmol/L at the end of the study.

The results of the study conducted by Thieden et al. showed that even tanning units that emit only 0.5 % or 1.4 % UVB are efficient to induce vitamin D synthesis. However, only exposure to 1.4 % UVB devices resulted in substantial increase in serum 25(OH)D concentrations (41). After 8 exposures (total dose 253 mJ/cm^2 of CIE vitamin D weighted UV (~21 SED) serum 25(OH)D concentrations increased by 30 nmol/L, reaching levels of 75 nmol/L. The daily CIE vitamin D dose for this group was slightly higher than was given in our last study (140 J/m^2 vs. 91 J/m^2, respectively), and corresponds to 9 minutes of whole body sun exposure at Oslo latitude. In the 0.5 % UVB group serum 25(OH)D concentrations increased by 15 nmol/L (total dose 49 mJ/cm^2 of CIE vitamin D weighted UV) (**Table 5. Part II**).

In contrast to other studies, Carbone at al. observed a large increase in serum 25(OH)D in volunteers exposed to 1.5% UVB tanning unit (total dose 20-40.5 SED over 12 weeks) (284). Just after 6 weeks serum 25(OH)D concentrations in participants with initial values < 75 nmol/L increased by 60 nmol/L, and by 18 nmol/L in persons with initial concentrations ≥ 75 nmol/L (**Table 5. Part II**).

10.1.3. Broadband and narrowband UVB devises. Other sources of UVB radiation used for treatment of psoriasis and other skin diseases are broadband UVB lamps (BB-UVB) and narrowband UVB lamps (NB-UVB). These lamps have fluence rates in the region of 280-360 nm, with a peak at 313 nm (BB-UVB) and of 311-313 nm (NB-UVB). In a number of recent studies both BB-UVB and NB-UVB were shown to induce significant vitamin D synthesis (**Table 5. Part III**) (164;285-293). The increase in serum 25(OH)D concentrations seems to be higher in the BB-UVB treated patients than in the NB-UVB treated patients. This might be due to the fact that spectra of NB-UVB lamps have a peak at 311-313 nm, while the maximal vitamin D synthesis occurs at wavelengths between 295 and 305 nm (39). Thus, BB-UVB

lamps cover most of the wavelengths required for vitamin D synthesis. The average increase of serum 25(OH)D concentrations for BB-UVB treated patients was 48 nmol/L, and for NB-UVB treated patients was 34 nmol/L (calculations are based on 8 published studies presented in **Table 5. Part III**).

10.1.4. What is the most efficient source of vitamin D? NB-UVB and BB-UVB lamps are the most efficient sources of vitamin D. They emit mainly UVB of very high intensity, and 1 MED dose may be achieved within few minutes of exposure (51).

The relative efficiency of other UVB sources to induce vitamin D synthesis varies with the ratio between UV_{Ery} and UV_D, which practically reflects UVB content (42). Tanning units that emit 5 % $UVB_{280-320\ nm}$ would most probably induce similar vitamin D synthesis as sun exposure at midday during the summer (UV_D/UV_{Ery} = 1.7-1.8) (40;42;283). However, commercially available tanning units in Norway emit high doses of UVA and contain only about 2 % or less $UVB_{280-320\ nm}$ (UV_D/UV_{Ery} < 1.3) (282). That means that less vitamin D may be produced after exposure to the same UV_{Ery} dose in tanning units than in the sun at midday during the summer. The UVB content of the solar radiation also varies during the day, being highest at noon (46). Thus, the effects of available tanning devices to induce erythema and vitamin D synthesis are similar to that of solar radiation early in the morning (7-8 a.m.) and after noon (4-5 p.m.) (46). The action spectra of vitamin D, of erythema, and of melanogenesis are within the limits of error similar (44). The main possible difference is that the vitamin D spectrum has no significant value in UVA. Thus, tanning units are, as we have estimated, slightly, more erythemagenic than vitamin D-producing, although the differences are probably not significant. Thus, the efficiency of different UVB sources to induce vitamin D synthesis is as following: NB-UVB and BB-UVB > solar radiation between 8 a.m. and 4 p.m. during the summer > commercially available tanning devices.

10.1.5. Indoor tanning and risk for cutaneous malignant melanoma (CMM). Several recent publications reported increased risk of CMM in indoor tanners (294). The OR presented by Lazovich et al. was 1.74 (CI, 1.42-2.14) for ever use of tanning facilities (295). A slightly lower RR for CMM in indoor tanners was found by Veierød et al. in Scandinavia (294). Earlier studies, however, do not support this, in spite of the fact that older tanning units were stronger than modern ones (282;296). Awareness about possible CMM risks should be high among sun bed users, especially those with fair-skin (skin type 1) (297). However, it is also possible that the risk of CMM for indoor tanners is overestimated due to other contributing factors, such as sunburns (298). A sun seeking behavior among these persons, recall bias present in retrospective studies.

According to Lazovich et al., the risk of CMM was also higher for users of UVA-emitting devices (OR 4.44; CI, 2.45-8.02) compared to UVB-enhanced units (OR 2.86; CI, 2.03-4.03) (295). The Setlow's CMM spectrum weights UVA strongly, which may support the epidemiological findings (299). However, the most recent CMM studies, using fish, transgenic mice, or monodelphis domestica, indicate that UVA has no melanomagenic effect (300-302). If these reports are correct and can be translated to humans, they argue against the recent reports of tanning units as CMM-generating devices. Two large meta-analyses also failed to show any significant positive correlation between use of tanning equipment and risk of CMM (RR 1.04 (CI, 0.91-1.14) (303) and RR 1.15 (CI, 1.00-1.31) (296)). Thus, the matter is still not scientifically solved.

Table 5. Part I Effect of UV exposure during the summer on serum 25(OH)D concentrations.

Author	UVB source Sun	Initial 25(OH)D, nmol/L	Total UV dose	E-BSA[2]	Final 25(OH)D (Δ25(OH)D), nmol/L
Thieden et al. 2009 (41)	Denmark (56°N) May-September	Was not estimated Indoor and outdoor workers	156 SED (1.4 SED daily for 121 summer days)	Real live conditions	82.2 in September, decreased to 56 in following February
Webb et al. 2010 (140)	Manchester, UK (53°N) March 2007-February 2008	45.8 (~48% < 50)	3.7 SED weekly during spring and summer	Real live conditions	71 (25.2) in September, decreased to 46 in following February
Burgaz et al. 2009 (142)	Sweden (60°N) January-September 2006	72 (18% < 50)	Weekly sun exposure: ≤ 3 hours (7%); 3-6 hours (33%); ≥ 6 hours (60%)	Real live conditions	99 (27) (sun seeking behavior 126 vs. 86 sun avoidance)
Osmancevic et al. 2009 (146)	Climate therapy, Gran Canaria (27°N), March 2006	57.2 (30% < 50)	166 SED over 15 days	whole body[1]	104.5 (47.3)
Vähävihu et al. 2008 (281)	Climate therapy, Gran Canaria (27°N), January - March 2005	42.7 (74 % < 50)	60.2 SED or 109 SED over 15 days	whole body[1]	56.4 (13.4) in 60.2 SED group; 62.3 (24.0) in 109 SED group
Azizi et al. 2009 (144)	Beer Sheva, Israel (31oN), December - November	64.8 (outdoor workers) ; 51.0 (indoor workers)	Outdoor workers: 4,4 hours (4-37 SED/d) Indoor workers: 0.9 hours (0.6-8.2SED/d)	Real live conditions	74 (9.2) in outdoor workers; 66 (15) in indoor workers
Barger-Lux et al. 2002 (145)	Omaha, Nebraska, (41°N) August-September, February-March	outdoor workers	544 hours during summer 16 weeks (38 hours per week)	Real live conditions	122 in late summer, decreased to 74 during following winter

[1] Whole body except for areas covered by underwear
[2] Exposed Body Surface Area

Table 5. Part II Effect of the exposure to tanning devices on serum 25(OH)D concentrations

Author	UVB source Tanning unit	Initial 25(OH)D, nmol/L	Total UV dose	E-BSA[2]	Final 25(OH)D (Δ25(OH)D), nmol/L
Porojnicu et al. 2008 (283)	Life Sun S 100 W (3.9 % UVB) January-April 2006	65 (20 % <50; 80 % <75)	8.5 MED (10 exposures over 4 weeks)	whole body[1]	92 (27), decreased almost to initial levels after 8 weeks
Moan et al. 2009 (52)	Solarium Super Plus 100 W (2.0 % UVB) January-April 2007	65 (40% <50)	6.8 MED or 13.5 MED (15 exposures over 7 weeks)	whole body[1]	80.2 (15) disregard of the UV dose
Lagunova et al. 2010 (43)	Gold Sun RS 100W + Beauty Sun S 25 W (2.2 % UVB) January-April 2008	48.4 (90% <75)	23.8 SED (10 exposures over 5 weeks) or 2,000 IU/d	whole body[1]	74 (25) after first intervention; 80.6 (31.2) after both interventions
Rhodes et al. 2010 (40)	Arimed B+Cleo Natural (5 % UVB) January –February	44 (62.5 % <50)	23.4 SED (1.3 SED x 3 per week for 6 weeks)	35% body	70 (26)
Thieden et al. 2008 (41)	Body Soft 410-220 (0,5% UVB) or Body Soft 364-220 (1,4% UVB) January-February	46.4 (57.6 % <50)	UV_D[3] 253 mJ/cm² or 49 mJ/cm² (6 min x 4 + 12 min x 4 over 16 days)	whole body[1]	1,4% UVB: 75 (29) 0,5% UVB: 62 (15)
Carbone et al. 2008 (284)	ETS (1.5 % UVB) February-March 2005	50 (<75) 122.5 (≥ 75)	20.2-49.6SED (0.84-1.69 SED (4-8 min) x 2 per week for 12 weeks)	whole body[1]	After 6 weeks: 110 (60) in <75; 140 (17.5) in ≥75 After 12 weeks: 135* in <75; 152.5* in ≥75

* After 12 weeks serum 25(OH)D also increased in control groups
[1] whole body except for areas covered by underwear
[2] Exposed Body Surface Areas
[3] CIE vitamin D weighted UVB dose

Table 5. Part III Effect of the exposure to narrowband and broadband UVB lamps on serum 25(OH)D concentrations

Author	UVB source — Narrowband and broadband UVB lamps	Initial 25(OH)D, nmol/l	Total UV dose	SE-BSA[2]	Final 25(OH)D (Δ25(OH)D), nmol/L
Osmancevic et al. 2007 (286)	Broadband UVB (TL-12), autumn-spring	92 (42 % <75)	0.9 J/m² over 8-12 weeks	whole body[1]	149 (57)
Armas et al. 2007 (164)	Broadband UVB, November-March	60.3 (90% <80) both blacks and whites	0.24-0.96 J/cm² (12 exposures over 4 weeks)	whole body[1]	(dose dependent increase: 6 SED - 53; 4-5 SED – 29.2; SED - 8)
Bogh et al. 2009 (285)	Broadband UVB (TL-12), January -March 2008	36.5 (67% <50); 27.8 (worshippers)	12 SED (40 min: 3 SED x 4 exposures)	24% (chest, back) body	59.8 (23.3) 53.1 (25.3) in worshippers
Osmancevic et al. 2009 (288)	Narrowband UVB (Cotona 4), Broadband UVB (TL-12), November – June	87 (BB-UVB) 95 (BB-UVB)	12 J/cm² (BB-UVB), 37 J/cm² (NB-UVB) over 8-12 weeks	whole body[1]	138 (51) NB-UVB; 174 (79)BB-UVB
Ryen et al. 2009 (291)	Narrowband UVB (TL-01), October 2008 - February 2009	57.5 (34 % < 50)	22.5 J/cm² (18 exposures over on average 6 weeks)	whole body[1]	125 (67.5)
Cicarma et al. 2009 (292)	Narrowband UVB (TI-01), November 2006-April 2007	66 (< 80); 112 (≥ 80)	6.9 J/cm² over 4 weeks	whole body[1]	110.8 (44.8) in < 80; 120.6 (8.6) in ≥80
Vähävihu et al. 2010 (293)	Narrowband UVB (TI-01), January-March 2008, 2009	43.2 (79 % < 50)	8.88 J/cm² over 15 exposures	whole body[1]	116 (73)
Vähävihu et al. 2010 (287)	Narrowband UVB (TI-01), December-March 2004-2006	42.1 (77 % < 50)	13 SED over 7 exposures	whole body[1], head and arms, abdomen	Whole body 55.8 (11.4); head and arms 48.8 (11.0); abdomen 39.2 (4.0)

SED for 100 J/m² = 10 mJ/cm² = 0.01 J/cm²
[1] Whole body except for areas covered by underwear
[2] Exposed Body Surface Are

10.2. Obesity and overweight are predictors of low vitamin D status

Obesity is a known risk factor for vitamin D deficiency. The key mechanism behind that is possibly increased sequestration of fat-soluble vitamin D in a large volume of fat tissue (61;190;208;211). However, other factors, such as low sun exposure and inadequate vitamin D intake, may also contribute to low vitamin D status in overweight and obese persons (194;196;209;210).

Low serum 25(OH)D concentrations result in elevation of PTH and often in sHPT (10;14;211). That might be necessary to maintain serum $1,25(OH)_2D$ concentrations high even in a setting of vitamin D deficiency. Supporting this theory, earlier investigations showed that persons with excess body weight had a low vitamin D status, but had high $1,25(OH)_2D$ levels (197;198;205;206). We have conducted a study in over 2,000 overweight and obese persons registered in a Metabolic and Medical Lifestyle Management Clinic in Oslo between September 2001 and January 2007 (Paper 2 and 3). The aim of the study was to investigate possible predictors of serum $1,25(OH)_2D$ concentrations, such as BMI, body composition, gender, age, season of blood sampling, and vitamin D status. The results of our study indicate that serum 25(OH)D may be the main predictor of serum $1,25(OH)_2D$ in overweight and obese adults (Paper 2) (**Figure 12**). We further showed that a decrease in 25(OH)D by 1 nmol/L was associated with a decrease in $1,25(OH)_2D$ concentrations by 0.4 pmol/L (P<0.001).
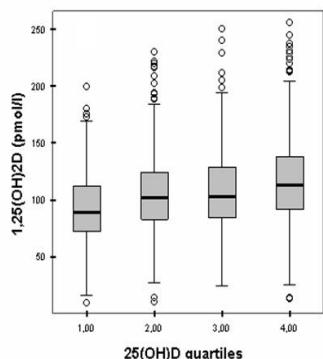

Figure 13. Serum $1,25(OH)_2D$ concentrations (pmol/L) grouped according to 25(OH)D quartiles. The box represents the 75th and 25th percentiles and the line within the box indicates the median quartile value. The whiskers correspond to minimum and maximum quartile values that are not classified as outliers. The circles above and below whiskers indicate outliers. The $1,25(OH)_2D$ concentrations were highest in the highest 25(OH)D quartile (one-way ANOVA p<0.001)

This is in agreement with other recent studies that report a significant positive correlation between serum 25(OH)D and $1,25(OH)_2D$ (120;128;194;200;207). Moreover, an increase of serum 25(OH)D concentrations after UVB exposure or vitamin D supplementation led to a subsequent increase in serum $1,25(OH)_2D$ concentration as well (146;182). These findings support the hypothesis that renal $1,25(OH)_2D$ synthesis is dependent on the availability of 25(OH)D, which is its precursor However, this might be different for children and adolescents that do not seem to have any correlation between serum 25(OH)D and $1,25(OH)_2D$ concentrations (Paper 3).

Despite of high prevalence of vitamin D deficiency in a teenage group (13-19 years), the highest serum $1,25(OH)_2D$ levels were observed in adolescents and the levels decreased significantly with age (Paper 2 and 3). This may at least in part be explained by age-related decrease in PTH capacity to induce expression of renal 1ά-hydroxylase (304), but may also be related to more strict regulation of renal $1,25(OH)_2D$ synthesis in children than in adults, since stabile $1,25(OH)_2D$ levels are essential during maximal bone growth (305).

Excess body weight is also unlikely to affect serum $1,25(OH)_2D$ concentrations in children and adolescents, but may be related to low vitamin D status (Paper 3). Our findings are in agreement with most studies in obese children (136;305-307).

In adults both $25(OH)D$ and $1,25(OH)_2D$ concentrations are associated with adiposity, BMI, age, and varied with the season (Paper 2). Thus, persons with high BMI had both low vitamin D status and low $1,25(OH)_2D$ concentrations (**Table 7**). Serum $25(OH)D$ concentrations were about 25-30 nmol/L higher during the summer than in the winter or early spring, with the highest values (> 80 nmol/L) observed in August. Serum $1,25(OH)_2D$ concentrations had apeak in May and another one in September. Winter $1,25(OH)_2D$ values were on the average 15 pmol/L lower than summer levels. The spring increase in $1,25(OH)_2D$ may possibly be mediated by high PTH that usually shows a strong negative correlation with $25(OH)D$, and the second one occurred after the $25(OH)D$ increase and was possibly driven by that increase. Thus, serum $1,25(OH)_2D$ concentrations are associated with a number of contributing factors which are closely related to each other, and may to a certain extent explain the $1,25(OH)_2D$ variability.

Table 7. Serum $25(OH)D$ and $1,25(OH)_2D$ concentrations in normal weight, overweight, obese, and morbidly obese adults (age 20-80 years).

BMI, kg/m^2	n	$1,25(OH)_2D$ ($\pm$ SEM), pmol/L	25(OH)D, nmol/L			
			Mean ($\pm$SEM)	% < 50	% < 75	>100
Men						
< 25	31	117.1 (6.6)	82.9 (3.3)	0	38.7	19.4
25-29.9	76	109.9 (8.5)	74.4 (4.3)	19.7	55.3	18.2
> 30	208	100.3 (2.2)	64.0 (1.6)	27.4	71.2	6.7
> 40	44	97.3 (4.7)	52.9 (2.9)	43.2	93.1	2.3
Women						
< 25	177	116.3 (3.2)	82.6 (2.0)	9.1	42.9	27.0
25-29.9	402	111.8 (1.8)	76.7 (1.2)	13.7	47.8	15.7
> 30	887	102.2 (1.2)	69.5 (0.8)	20.9	62.3	11.3
> 40	158	97.9 (2.8)	65.1 (2.0)	27.2	68.0	8.2

Vitamin D deficiency in children may be related to increased risk of MS, T1D, and asthma (305). In adults, a low vitamin D status may be associated with several common diseases, including cancer, autoimmune diseases, diabetes, cardiovascular events and total mortality (3;17;107). Based on our studies, we may conclude that since persons with excess body weight have high prevalence of vitamin D deficiency and insufficiency, they may also be more predisposed for the above mentioned diseases.

Moreover, a decrease serum $1,25(OH)_2D$ may possibly also contribute to increased risk of cardiovascular diseases, diabetes, and renal failure in obese and overweight individuals (308). Interestingly, the best prognosis for cancer survival in our studies was observed for patients that were diagnosed with cancer during late summer and early autumn when both serum $25(OH)D$ and $1,25(OH)_2D$ concentrations are high (139;251-256).

10.3. Excess body weight, vitamin D, and cancer

Body composition and BMI are important predictors of vitamin D status. Our earlier investigations suggested that 5 kg/m^2 BMI increase was related to about 5 nmol/L decrease in serum $25(OH)D$ concentrations (128). Excess body weight is also associated with cancer incidence and mortality, with about 3-8 % of the total cancer incidence possibly being attributed to excess BMI (309;310).

In U.S. Health Professionals Follow-up Study Giovannucci et al. has observed that the risk of several types of cancer including PCa were modified by BMI and serum $25(OH)D$ (88), while BMI correlated negatively with $25(OH)D$ values. The study performed by Tuohimaa et al. revealed an interaction between methabolic syndrome factors, including BMI, vitamin D status, and PCa risk (311). Thus, the effect of metabolic factors on PCa risk was strongly conditioned by $25(OH)D$ levels.

Based on these finding, we proposed a hypothesis that the increased risk of cancer in persons with overweight and obesity may possibly be related to decreased serum $25(OH)D$ concentrations (Paper 1). Our calculations were performed based on current meta-analysis by Gorham et al. (312) and Garland at el. (313) that reported 50-55 % decrease in CRC and BCa risk with 55 nmol/L $25(OH)D$ increase, and the assumption that the effect of vitamin D status may be similar in all vitamin D-sensitive cancer types (Paper 1).

According to our calculations, low serum $25(OH)D$ concentrations may explain approximately 20 % of total cancer risk attributed to high BMI. However, the contribution of vitamin D status to obesity-related cancer risk may vary with cancer type, probably being highest for CRC in women and BCa (Paper 1). Supporting our hypothesis, poor BCa outcomes and survival were linked to low vitamin D concentrations as a consequence of excess body weight in the study of Tsvetkova et al. (314). The authors evaluated the relationship between vitamin D and obesity-related factors in RCT of BCa adjuvant chemotherapy, and concluded that serum $25(OH)D$ concentrations were associated with key obesity-related factors, season of blood sampling, and race (314). Nonetheless, the prognostic effects of obesity-attributed low vitamin D status cannot be evaluated yet, since the follow-up of the study is not completed.

An interesting observation was reported by Yu et al. who investigated the effect of dietary vitamin D_3 on endometrial cancer (ECa) development in mice (92). Animals were fed high-caloric diet to induce obesity, and the study group got diet additionally fortified with vitamin D_3. Obese mice had increased risk of ECa, which was modified by vitamin D. Dietary vitamin D inhibited the carcinogenic effect of obesity on ECa, and was associated with 25 % reduction in incidence of endometrial pathology in obese mice ($P < 0.001$) (92). The effect was explained mainly by the ability of vitamin D to reverse the obesity-induced increase in osteopontin and decrease in E-cadherin.

Serum $25(OH)D$ concentrations may also affect circulating leptin levels (315), inflammatory markers (308), modulate glucose intolerance and insulin resistance (316;317), which are all factors contributing to increased risk of cancer in overweight and obese persons

(318). Additionally, low serum $1,25(OH)_2D$ levels, common in this group of patients, were recently linked to excess midterm mortality in patients with coronary heart disease, hypertension, diabetes, heart and renal failure (128;308). Moreover, serum 25(OH)D and $1,25(OH)_2D$ seem to be independent predictors of all-cause and cardiovascular mortality (319-321), and survival from some vitamin D-sensitive cancers (322).

11. CONCLUSIONS

The aim of this work was to investigate the impact of vitamin D predictors (UV exposure, BMI, vitamin D intake) on vitamin D status and cancer risk.

The effect of UV exposure and vitamin D intake on serum 25(OH)D concentrations were evaluated in interventional studies. We have simulated a Norwegian summer by exposure to commercial, UV-emitting tanning units (two types) with ~2 % of $UVB_{280-320nm}$. We have also compared the efficiency of high dose oral vitamin D supplementation with moderate exposures to these tanning devices with respect to achieving a given increase in serum 25(OH)D concentrations. Thus, based on interventional studies we may conclude that:

- ❖ Moderate UV exposures given over 5-7 weeks may raise serum 25(OH)D concentrations from typical winter values to typical summer values.
- ❖ The recommended by Holick sun exposure (¼ MED (~0.5-0.8 SED) daily to ¼ body skin surface) is most probably too small to provide optimal vitamin D status (25(OH)D ≥ 75 nmol/L).
- ❖ The increase in serum 25(OH)D concentrations is dependent on initial vitamin D status: persons with the lowest baseline 25(OH)D concentrations have the largest increase. However, persons with vitamin D deficiency (25(OH)D < 50 nmol/L) do usually not reach vitamin D sufficiency (25(OH)D ≥ 75 nmol/L) after the mentioned UV exposure.
- ❖ An oral vitamin D intake of 2,000 IU is almost equal to a whole body sun exposure of ~0.2 MED (0.5-0.8 SED) corresponding to 5-7 minutes midday on a midsummer, cloudless day in Oslo.

The associations between body composition, BMI, and $1,25(OH)_2D$ concentrations were analyzed in 1779 adults and 102 children with overweight or obesity. The following conclusions were drawn:

- ❖ The prevalence of vitamin D deficiency and insufficiency is increasing with BMI. Around 60-70 % of obese adults (BMI > 30 kg/m^2) and 50 % of overweight and obese children have serum 25(OH)D < 75 nmol/L.
- ❖ In adults, the serum 25(OH)D concentration is the strongest predictor of serum $1,25(OH)_2D$ concentration. A decrease in 25(OH)D by 1 nmol/L is associated with 0.4 pmol/L decrease in serum $1,25(OH)_2D$.
- ❖ There is no correlation between serum 25(OH)D and $1,25(OH)_2D$ concentrations in children and adolescents with excess body weight.
- ❖ Serum $1,25(OH)_2D$ concentrations decrease with increasing BMI and adiposity. Older persons (> 50 years) have lower $1,25(OH)_2D$ concentrations than younger persons (< 30 years).

❖ Serum 25(OH)D and 1,25(OH)$_2$D concentrations vary during the year. In obese and overweight adults there is a late summer peak for both serum 25(OH)D and 1,25(OH)$_2$D concentrations.

We have also estimated possible contribution of obesity- related decrease in serum 25(OH)D concentrations on cancer risk. According to our calculations:

❖ At least 20 % of the total cancer risk attributable to high BMI may be explained by low vitamin D status.
❖ The contribution of vitamin D status to obesity- related cancer risk is different for different cancer types.
❖ A low vitamin D status may explain 40 % of obesity-related risk BCa, and 26 % and 75 % of obesity-related CRC risk in men and women, respectively.

12. FUTURE PERSPECTIVES

Over 300 clinical trials have been initiated recently to investigate the association between vitamin D status and cancer risk and survival (277;296). However, most of them are not yet accomplished. The results of these and other clinical trials will hopefully clarify the relationship between serum levels of vitamin D metabolites and cancer development and prognosis. Phase II and Phase III RCT are needed to elucidate the potential role of vitamin D metabolites and analogues in anti-cancer treatment. We plan to continue our work in this field and to investigate vitamin D status in the Norwegian cancer population linking it to cancer risk and prognosis.

New guidelines for vitamin D supplementation and sun exposure are required in order to improve vitamin D status, both on individual and population levels. The recommended vitamin D intake and sun exposure should be reconsidered and, according to the present work, increased significantly. We aim to continue our work in developing these recommendations.

In light of recent research, the regulations about UVB content in commercially available tanning units should be changed. Further research is needed in order to estimate possible impact of sun bed use on CMM risk.

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LIST OF CORRECTIONS

1. Abbreviations (25-**H**ydroxymin D, **DBP**, SED – Standard Er**y**thema Dose) have been corrected.
2. Table 6 appears now in the text as **Table 5**.
3. Table 7 appears now in the text as **Table 6**.
4. Table 5 appears now in the text as **Table 7**.
5. **FUTURE PERSPECTIVES** chapter is added in the thesis.

3

Effect of vitamin D supplementation and ultraviolet B exposure on serum 25-hydroxyvitamin D concentrations in healthy volunteers

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Abstract

Solar UV radiation and food are the two naturally available and major sources of vitamin D for humans. At northern latitudes sun exposure provides enough vitamin D only during the summer. During the winter vitamin D intake becomes the most important source of vitamin D. Indoor tanning units are good sources of vitamin D as well, but their use are being debated because of the skin cancer risk associated with large exposures. The aim of the present study was to compare the efficiency of oral vitamin D_3 supplementation (2000 IU/d for 30 days) and 10 sun bed exposures of total dose 23.8 SED (vitamin D weighted dose 319 mJ/cm^2) to improve the vitamin D status. Healthy volunteers were randomized into two groups: Group 1 received vitamin D supplementation at first and then continued with 10 whole body exposures. Group 2 started with 10 exposures and than continued with vitamin D supplementation. The oral supplementation with vitamin D_3 was slightly more beneficial than exposure to UVB and resulted in serum 25(OH)D increase by 27.5 nmol/L (SEM ± 3.5 nmol/L; P<0.01) vs. 22.9 nmol/L (SEM ± 5.0 nmol/L; P<0.01) in the UVB group. At the end of the study the pooled serum 25(OH)D increase was 31.3 nmol/L (SEM ± 3.8 nmol/L; P<0.001), and 61 % of the volunteers had serum 25(OH)D ≥ 75 nmol/L. Thus, a daily whole body exposure to 0.5 SED may be enough to achieve and maintain serum 25(OH)D concentrations ≥ 75 nmol/L. This dose almost equals to 2000 IU/d of oral vitamin D supplementation, and about 2 hours of sun exposure weekly to 1/3 skin surface area at Oslo latitude around midday during the summer.

Introduction

Solar UVB radiation is the main source of vitamin D for humans (1). About 80-90% of total vitamin D is produced in the skin (1). Exposure of the whole body to the sun for 1 minimal erythema dose (MED) (~2.5-3.5 standard erythema dose (SED)) under optimal conditions may be equivalent to 10 000 -25 000 IU of oral vitamin D (2). However, vitamin D synthesis is a self-regulated process, and under prolonged sun exposure both previtamin D and vitamin D are degraded to tachysterol and other photoproducts (2). Thus, excessive sun exposure does not result in vitamin D intoxication as was once thought, but it may cause DNA damage and sunburn and, thus, increase the risk for skin cancer (3).

The sun exposure time needed for optimal vitamin D synthesis vary greatly with time of day, season, latitude, altitude and weather conditions (4-6). At Oslo latitude, 59^0N, vitamin D is produced in the skin only during the summer months (April – October) with the maximum vitamin D synthesis around noon 11 a.m. - 1 p.m. (7). Between November and March practically no synthesis of vitamin D occurs due to lack of UVB in solar radiation. Therefore, vitamin D supplementation is recommended during the winter to maintain a good vitamin D status (8). The recommended daily dose of vitamin D in Norway is 300 - 400 IU (7.5 - 10μg) (9). This is, according to recent literature, hardly enough to keep serum 25(OH)D concentrations >50 nmol/L (10). Artificial sources of UVB may also be good sources of vitamin D during the winter, however little is known how given doses of UVB radiation correspond to given doses of vitamin D supplementation, with respect to efficiency to increase serum 25(OH)D (11;12).

In a previous study, we found that 10 sun bed exposures (total dose of 8.5 MED) were enough to reach summer serum 25(OH)D concentrations (12). A vitamin D supplementation of 200 IU per day following the exposures was far too little to maintain the achieved serum 25(OH)D values (12). The present study was designed to investigate if a vitamin D supplementation with 2000 IU daily (tolerable upper limit for vitamin D intake according to the European Commission (13)) is efficient to remain serum 25(OH)D levels achieved after 10 sun bed exposures. We also aimed to investigate if the initial vitamin D status effects the efficiency of UVB irradiation to increase serum 25(OH)D levels.

Materials and methods

Volunteers

A total of 31 healthy volunteers (8 men and 23 women), aged between 23 and 61 years, were recruited in the study. All volunteers were living in Oslo (59°N).

The participants were asked to fill out questionnaires with questions about age, weigh, height, skin type, sun exposure and indoor tanning habits. The questionnaires contained also questions about dietary vitamin D intake with food and/or supplements. The exclusion criteria were: the presence of severe disorders and medical conditions known to effect vitamin D status; pregnancy or plans to become pregnant; high-dose vitamin D supplementation, winter vacations to southern latitudes and indoor tanning for 8 weeks before initiation of the study or plans for traveling to southern latitudes during the study.

The study was approved by the Regional Ethical Committee. Each participant gave written informed consent.

UVB source

The source of UV radiation was a commercially available and approved type 3 sun bed (2,15% UVB: 280-320 nm), equipped with Golden Sun RS 100 W and Beauty Sun S 25 W spaghetti tubes (Wolff System, Basel, Switzerland). The emission spectra of the sun bed and the sun (Oslo, 22 July 2010, 12.00 AM) were measured with a AvaSpec ULS fiber optic spectrometer using AvaSoft 7.3.1 (Avantes BV, NL-6961 RB Eerbeek, Netherlands) (Figure 1 A). Efficiency spectra of vitamin D formation were calculated based on action spectra of previtamin D_3 synthesis in the human skin by Holick et al. (Figure 1 B) (14). CIE-weighted UV doses are presented as Standard Erythema Dose (SED; 1 SED = 100 J/m^2). The SED is equivalent to about 0.5 MED for the most sensitive type 1 skin (1 MED = 200 J/m^2) (4).

Design and protocol of the study

The study was carried out during the winter months (January - March) in order to avoid any 25(OH)D contribution from solar radiation. All volunteers were recruited between December 2007 and February 2008. The study extended over 9 weeks.

The participants were randomly assigned into two groups (Figure 2). Group 1 (n_0=15) received 2000 IU (50μg) of vitamin D_3 (J.R. Carlson Laboratories, Inc**.,** IL 60004-1985) daily for 30 days, then continued with 10 whole body sun bed exposures (1.- 7 min (1.3 SED); 2-3.- 10 min (1.9 SED); 4-5.-13 min (2.4 SED); 6-10.- 15 min (2.8 SED)) twice a week with a total dose of 23.8 SED (vitamin D weighted: 134 J/m^2 per 1 SED). Group 2 (n_0=16) started with 10 sun bed exposures following the same exposure schedule as

Group 1 with a total dose of 24 SED, then continued with 2000 IU (50μg) of vitamin D_3

daily for 30 days. Individual MED were determined at the baseline to avoid any sun

burns. Four skin areas (2x2cm) on the anterior forearm were exposed to different doses of

UV (10 – 15 – 20 –25 min). The skin reaction was evaluated 24h after exposure.

Blood sampling and methods of analyses

Blood samples were taken at the baseline, after first intervention (vitamin D

supplementation (Group 1), after 10 sun bed exposures (Group 2)) and at the end of the

study. Serum was separated from the blood cells by centrifugation and then frozen to

−20 °C. All serum samples in batch were analyzed in Haukeland University Hospital,

Bergen, Norway. The 25(OH)D assay was performed by liquid chromatography-mass

spectrometry method (LC∕MSD SL; Agilent Technology, CA).The assay was performed

according to a modified version of the method described elsewhere (11). The mean

recovery of 25(OH)D was 77.2% (SD 3.9%) and the interassay variation was 4.9%, with

a detection limit < 4 nmol/l.

Statistical analysis

The data were analyzed using Sigma Plot 10.0 for Windows. The values of the variables

were presented as means ± SEM. The criterion for statistical significance was defined as

$P < 0.05$.

Results

The spectral characteristics of the sun bed used in the study and that of the midday,

midsummer sun are shown on Figure 1A. According to our calculations, based on

efficiency spectra of previtamin D_3 formation of these two UVB sources, the sun bed was about 25-30 % less efficient in producing previtamin D_3 than the sun.

Of the 31 volunteers recruited in the study, 25 subjects completed the second phase of intervention (Figure 2). Four persons withdrew from the study during the supplementation part and two persons during the sun bed treatment for reasons unrelated to the interventions. No side-effects were observed.

The baseline characteristics of the two groups are shown in Table 1. There was no significant difference in mean age, BMI, vitamin D intake or serum 25(OH)D concentrations at baseline between the groups, although volunteers in Group 1 had 8.2 nmol/L higher serum 25(OH)D than those in Group 2. The mean serum 25(OH)D concentration at baseline for the whole group was 50.2 ± 3.61 nmol/L. Only 3 persons (10%) had serum 25(OH)D > 75nmol/L. Serum 25(OH)D concentrations < 50nmol/L were observed in 15 volunteers (50%).

After the first phase of intervention serum 25(OH)D concentrations increased significantly in both groups (P<0.01) (Figure 3). Serum 25(OH)D concentrations increased by 27.5 ± 3.48 nmol/L in Group 1 after vitamin D_3 supplementation and by 22.9 ± 3.48 nmol/L in Group 2 after 10 sun bed exposures (P = 0.49) (Figure 4). The second phase of intervention resulted in a slight and non-significant further increase in serum 25(OH)D (Figure 3, 4). This is to be expected since serum 25(OH)D concentrations usually plateau after 4-6 weeks of intervention (15;16). The total increase was similar in both groups (Figure 4, Table 1). Although the serum 25(OH)D concentrations at the end of the study were highest in Group 1, the relative increase was similar in both groups (Table 1).

The absolute increase was also similar in participants with baseline serum 25(OH)D concentrations < 50 nmol/L and > 50 nmol/L (Figure 5). However, the achieved serum 25(OH)D concentrations were highest in the group with high baseline 25(OH)D (Figure 5).

The increase in serum 25(OH)D in Group 2 after the first phase of intervention (10 sun bed exposures) was to some extent greater in persons with low BMI compared than in persons with high BMI, but not significantly (data not shown). No correlation between absolute increase in serum 25(OH)D and BMI was observed after vitamin D supplementation. This might be due to rather small differences in BMI between volunteers. The majority of participants had BMI within the normal range (18-24.9 kg/m^2), or were overweight (BMI 25-29.9 kg/m^2). Only one volunteer had BMI > 30 kg/m^2.

Discussion

Although there is no consistent definition of vitamin D deficiency, sufficient vitamin D status is usually defined as serum 25(OH)D concentrations ≥75 nmol/L (17;18). This cutoff point is based on evaluations of the biological effect serum 25(OH)D levels on serum concentrations of PTH levels and clinical data that supports a protective effect of vitamin D against a number of diseases (18;19).

Serum 25(OH)D concentrations vary with season with the lowest values observed during the winter and early spring (20). Our study shows that only 3 adults (10%) among 31 volunteers had sufficient vitamin D status in the middle of the winter (January 2008).

This is in agreement with other investigations that reported the prevalence of vitamin D sufficiency to be as low as 10-20% during the winter months (19;21).

In Norway and other northern countries the highest serum 25(OH)D concentrations were observed in July-September with the mean values above 60-80 nmol/L (21). The late summer 25(OH)D values predict the vitamin D status during the following winter monthes. It has been calculated by Webb at al. that a circulating 25(OH)D levels ≥80nmol/L at the end of the summer are required in order to maintain 25(OH)D values ≥50 nmol/L during the following winter (22). However, several recent studies found that current sun exposure habits do not provide for the required vitamin D status for most people (21-23). According to Christensen et al. only 44% of persons from Western Norway have serum 25(OH)D >75 nmol/L at the end of the summer (21). The results of the recent study performed in Greater Manchester, UK, indicate that exposure to 0.5 SED daily between 11 a.m. and 1 p.m. in real life conditions (typical summer clothing) is not enough to reach the level of vitamin D sufficiency at the end of the summer (22). Based on the results of our study, we may conclude that a whole body exposure to at least 0.5 SED (5-6 minutes) may be needed to reach and maintain an optimal vitamin D status. This is in agreement with the study conducted in Copenhagen, Denmark, that suggested the serum 25(OH)D concentrations ≥80 nmol/L in September may be achieved by daily sun exposure to 1.4 SED in real life conditions (24).

In order to maintain 25(OH)D ≥ 80nmol/L during the winter, vitamin D supplementation is recommended. Holick et al. reported that 1000 IU/d of vitamin D in the winter for 11 weeks was ineffective in raising the blood levels ≥ 75 nmol/L (16). According to the recent study by Cashman et al. 920-1640 IU may be required to keep

late summer 25(OH)D concentrations throughout the year if supplementation is started in the autumn (10). Thus, higher doses of vitamin D supplementation (2000-3000 IU) may be considered necessary to reach those values if supplementation is started later in the winter when initial levels are low (25). The response of serum 25(OH)D to each 100 IU vitamin D ingested vary from 2.5 nmol/L in persons with low initial levels to 1.5 nmol/L or less for those with high serum 25(OH)D at baseline (15;16).

Alternatively, artificial UV sources can be used to improve vitamin D status during the winter (11;26). However, little is known about any interaction between vitamin D supplementation and UV exposure necessary to improve and maintain 25(OH)D levels > 75 nmol/L.

According to Holick's rule: "Exposure of ¼ body skin surface to the sun for ¼ MED (~0.5-0.8 SED) at 42°N (Boston) in March would be equally efficient to 1000 IU (25μg) of vitamin D intake" (14). The exposure required for vitamin D production equal to 1000 IU oral intake is also called a standard vitamin D dose (SDD), and for skin type II person corresponding to a vitamin D weighted dose of 106-110 J/m^2 or, based on Holick's rule, to ~7 minutes sun exposure to ¼ of body surface at Oslo latitude (4;5). According to calculations performed by Webb and Engelsen for SDD at 62.5°N latitude (6), a person with skin type II to III would need to spend ~9-11 minutes in the sun at around 12:00 a.m. in order to reach SDD.

Our results suggest that not even a dose of 91 J/m^2 (vitamin D weighted) of whole body exposure is equivalent to 1000 IU vitamin D intake. Similar conclusions were drawn by Thieden et al., who has conducted a study on healthy volunteers with sun bed exposure in the daily dose of ~140 J/m^2 (vitamin D weighted) for 18 days (26). This

dose was exactly enough to increase serum 25(OH)D concentrations up to 75.3 nmol/L (26). Rhodes et al. also concluded that the recommended sun exposure can produce 25(OH)D concentrations $\geq$ 50nmol/L, but not the proposed sufficient 25(OH)D levels (27).

The effectiveness of UVB exposure to increase serum 25(OH)D concentrations may also be dependent on initial vitamin D status. As it has been shown by us and other investigators, low initial 25(OH)D concentrations were associated with large absolute and relative increases in serum 25(OH)D, irrespective of UVB dose (11;28;29). In the present study we have also observed this trend (Figure 5). However, adults who were vitamin D deficient did reach serum 25(OH)D levels $\geq$ 75 nmol/L after intervention.

Several studies have also suggested that genetic factors may explain the interindividual variation in serum 25(OH)D concentrations (30;31). In fact, genetic variations at specific loci may substantially affect vitamin D status. Recently, three such loci were identified. These are genes involved in cholesterol synthesis from 7-DHC, hydroxylation of vitamin D to 25(OH)D, and vitamin D transport (30). The combination of impaired alleles at all three loci more than doubles the risk of vitamin D insufficiency (30). Moreover, genetic predisposition may explain about 50% of variability in serum 25(OH)D during the summer (31). This can at least in part explain the discrepancy between calculated and actual UV dose required for optimal vitamin D production.

One should also remember that in the most models used for calculations of SDD a flat horizontal surface model (pancake model) was used (4-6). This model does not take into account the geometry of the human body and the surface of the skin that is not directly exposed to the sun. Thus, the time required to reach SDD may be longer than

predicted by the calculations. In the case of calculations for whole body exposure this time should be doubled, since only half of the body can be exposed to the sun at any time (29).

Besides season and time of the day, SDD may also vary largely with real atmospheric conditions, orientation of the skin surface and of sun screams use (4-6). From this point of view, use of indoor tanning units could be more controllable and beneficial than real sun exposure since whole body area can be exposed to UVB radiation of equal intensity. Whole body exposure will also reduce the time of sun or sun bed exposure required for an optimal vitamin D synthesis. However, a growing body of evidence suggests that the modern sun beds may increase the risk of skin cancer (32;33). This might be due to strong UVA radiation emitted by many sun beds, in some of them being 3-10 times stronger compared to the sun. At the same time, careful sun exposure does not seem to increase the skin cancer risk and still can be recommended to improve vitamin D status during the summer.

However, vitamin D supplementation may be the safest way for improving the vitamin D status. Based on the results of our study, oral vitamin D supplementation with 2000 IU is equally or more effective to increase serum 25(OH)D concentrations than 10 sun bed exposures. A daily supplementation with 2000 IU results in an increase of serum 25(OH)D by 25-30 nmol/L, which is in most cases enough to achieve and maintain vitamin D sufficiency. Thus, the recommended daily dose (400 IU) should be reconsidered and increased significantly. No vitamin D toxicity has been observed for vitamin D supplementation <10,000 IU (34).

Acknowledgments

Table 1

Characteristics of study population.

	Group 1	Group 2	*P* value
Vitamin D intake*, µg/day	6.7 ± 1.4	6.6 ± 1.0	0.98
BMI, kg/m2	23.3 ± 0.8	24.5 ± 1.0	0.33
Age, years	36.3 ± 2.9	39.3 ± 3.3	0.50
Skin type** I; II; III; IV	2;8;4;1	2;10;3;1	0.78
Initial 25(OH)D levels, nmol/L (SEM)	52.5 ± 4.0	44.3 ± 4.5	0.19
25(OH)D after FF[#], nmol/L (SEM)	80.9 ± 4.1	67.2 ± 4.9	0.05
25(OH)D after SF[¤], nmol/L (SEM)	84.8 ± 5.1	76.3 ± 6.2	0.32
Absolute 25(OH)D increase, nmol/L (SEM)	31.2 ± 5.0	31.3 ± 5.6	0.99
Relative 25(OH)D increase, %	66.5 ± 13.9	89.9 ± 24.3	0.44

*Self-reported vitamin D intake calculated based on food frequency questionnaire

**Self-reported skin type according to Fitzpatrick classification

[#]Fisrt phase, [¤]Second phase

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Figure 1

Spectral characteristics of the sun bed used in the study and of the sun at noon midsummer in Oslo (22 July 2010). Action (A) and efficiency (B) spectra of vitamin D_3 formation in the skin.
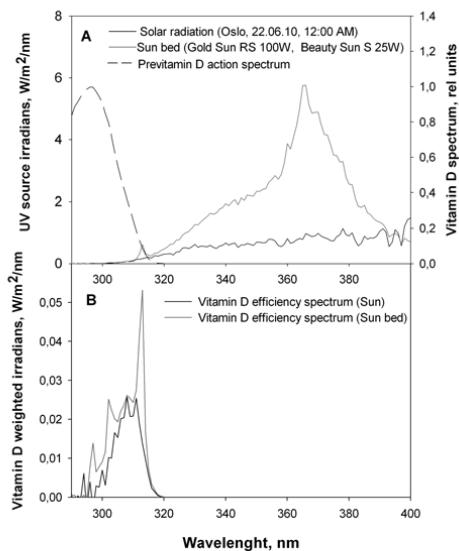
Figure 2

Diagram showing flow of subjects through the study and study design.

31 healthy volunteers
Baseline blood sample, $n_0 = 31$
Questioning, $n_0 = 31$

Randomisation

Group 1, $n_0 = 15$ Group 2, $n_0 = 16$

First Intervention (FI)

Vitamin D intake
2000 IU/day x 30 days
Blood sample, $n_1 = 13$

10 sun bed exposures
Total dose 23.8 SED
Blood sample, $n_1 = 16$

Second Intervention (SI)

10 sun bed exposures
(total dose 23.8 SED)
Blood sample, $n_2 = 11$

Vitamin D intake
2000 IU/day x 30 days
Blood sample, $n_2 = 14$

25 volunteers completed the study
6 volunteers withdrew due to
reasons unrelated to intervention
No side-effects were observed

Figure 3

Serum concentrations of serum 25(OH)D in two groups at baseline, after the first and the second phase of intervention. Data are means ± SEM. There was a significant increase in serum 25(OH)D during the first phase of intervention.
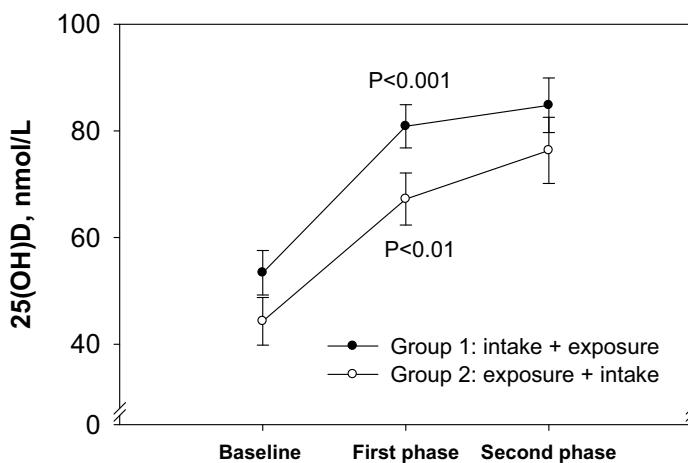
Figure 4

Absolute serum 25(OH)D increase after first and second intervention phases. Data are

means ± SEM.
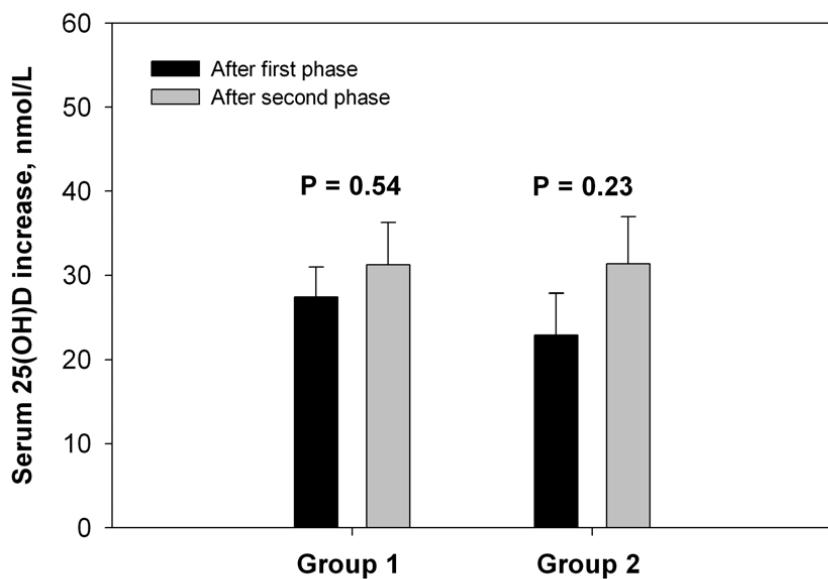
Figure 5

Serum 25(OH)D increase after two intervention phases in vitamin D deficient and non-deficient persons. Data are means ± SEM. Means with superscripts without a common letter differ, $P<0.05$.