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Impact of Air Pollution on Vitamin D Status and Related Health Consequences

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1. Introduction

During the last decade a growing interest in vitamin D-related problems can be observed and a few thousands of scientific publications are dedicated to this task every year.
The alarming statistical data regarding propagation of vitamin D deficiency in all continents and our developing knowledge about novel, non-calcemic actions of vitamin D seem to be two main causes of this phenomenon. Indeed, recent epidemiological studies suggest that worldwide prevalence of inadequate vitamin D status is higher than expected, however it may result from different factors, including geographical location and cultural background.
Since vitamin D skin synthesis, which takes place under the influence of the sun's ultraviolet B (UVB) radiation, covers as much as 90% of total body needs, inadequate radiation or insufficient cutaneous absorption of UVB are regarded as major causes of vitamin D deficiency.
Air pollution is a chief factor determining the extent of solar UVB that reaches earth surface and several epidemiological data, which represents different populations living in different geographic latitudes, indicate that atmospheric pollution (especially high tropospheric ozone content) may play a significant independent role in the development of vitamin D deficiency. As a result prevalence of D hypovitaminosis among urban residents can be more than twice higher than that of rural inhabitants.
The problem of vitamin D insufficiency has been underestimated for many years and it has been predominantly associated only with bone diseases. Discovery of vitamin D receptor and its identification in a wide number of tissues other than bones led to the designation of novel, so-called "non-calcemic" (e.g. antiproliferative and immunomodulatory), actions of cholecalciferol. Subsequently, there is a growing number of diseases and conditions, development and/or progression of which can be associated with inadequate vitamin D status, including different types of cancers, autoimmune disorders as well as cardiovascular events. Interestingly, prevalence of many of these diseases also positively correlates with the intensity of air pollution. Therefore one can conclude that with the increasing atmospheric pollution grows a number of people in the world who are vitamin D deficient or insufficient and indirectly exposed to several poor health outcomes.
This chapter gives an overview of the literature on this topic and assesses the available data about the association between air pollution, vitamin D status and prevalence of so-called civilization-related diseases. A general information regarding vitamin D metabolism is

given first. Next, current definitions of vitamin D status are presented, followed by the alarming statistical data about vitamin D deficiency pandemic and its correlation with the intensity of air pollution and prevalence of common human diseases. To understand possible mechanism linking vitamin D deficiency with these poor health outcomes, first a brief presentation of traditional (calcemic) and novel ("non-calcemic") actions of vitamin D is given. Subsequently, epidemiological and experimental data regarding the association between vitamin D status and prevalence of bone diseases, different types of cancers, autoimmune disorders and cardiovascular diseases is presented. Finally, therapeutic perspectives and general guidelines about vitamin D supplementation and requirements are included. The chapter ends with a short summary which facts about vitamin D can be generally accepted and which still require more solid scientific background.

2. Vitamin D metabolism

In mammals, vitamin D_3 (cholecalciferol) is either produced in the skin by the non-enzymatic conversion (photochemical cleavage) of provitamin D (7-dehydrocholesterol) to previtamin D_3 under the influence of ultraviolet radiation (290-315nm), or delivered from food sources. In the skin previtamin D_3 can also undergo isomerization that results in creation of biologically inactive compounds (lumisterol and tachysterol) and this mechanism prevents from the vitamin D_3 overproduction and intoxication after prolonged exposure to sunlight. In the liver vitamin D_3 undergoes enzymatic hydroxylation to 25-hydroxyvitamin D_3 ($25(OH)D_3$) in the reaction catalyzed by 25-hydroxylase (CYP2R1).
In the tissues that have 1α-hydroxylaze activity (predominantly in kidneys, but also in activated macrophages, colon, prostate, breast, brain as well as in other tissues), $25(OH)D_3$ is converted to the active vitamin D metabolite – $1,25(OH)_2 D_3$ (calcitriol), whereas hydroxylation in position 24 (by 24-hydroxylase – CYP24) initiates degradation of vitamin D metabolites (Horst & Reinhardt, 1997) [Figure 1]. Efficiency of renal vitamin D_3 hydroxylation is regulated by the level of calcium and phosphate ingestion, parathyroid hormone and, in a negative feedback, by circulating levels of $1,25(OH)D_3$. The extra-renal hydroxylation is determined by local factors e.g cytokines, growth factors as well as by $25(OH)D_3$ concentration, making it particularly sensitive to vitamin D deficiency (Marques et al., 2010).
The serum $25(OH)D_3$ concentration is the parameter of choice for the assessment of vitamin D status for several reasons. First of all, it reflects total vitamin D derived from dietary intake and sunlight exposure as well as the conversion of vitamin D from adipose stores in the liver. Furthermore, it is relatively stable and it has a long (2-3 weeks) half-life in circulation. Finally, it was shown in several epidemiological studies that $25(OH)D_3$ levels correlated best with several clinical conditions.

3. Definition and prevalence of vitamin D deficiency, insufficiency and adequacy

Definition of vitamin D status has evolved during the last decade. Whereas $25(OH)D_3$ level below 10 ng/μl (25nmol/l) is still, indisputably defined as vitamin D deficiency, the ranges of vitamin D sufficiency has been recently modified. For years, $25(OH)D_3$ levels between 10 ng/μl and 20 ng/μl have been identified as insufficiency (WHO report 2003), however with the recent changes in laboratory reference rages, nowadays vitamin D adequacy is defined as 30 to 76 ng/μl (75nmol/l) and $25(OH)D_3$ concentrations between 10 and 30 ng/μl are described as insufficiency. Vitamin D intoxication which is extremely rare, occurs when $25(OH)D_3$ concentrations exceed 150 ng/μl.

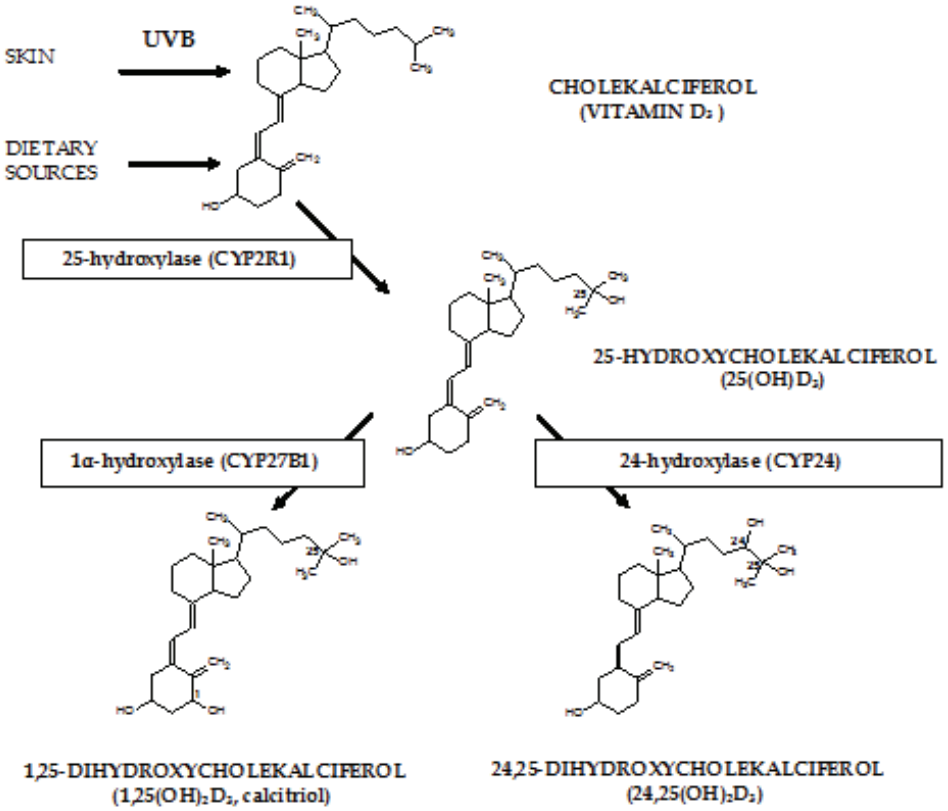

Fig. 1. The simplified scheme of the vitamin D synthesis
Cholekalciferol (synthesized in the skin upon the UV radiation or delivered with food undergoes several hydroxylations, firstly in the position 25 in the liver. The next hydroxylation catalyzed by the 1α-hydroxylase (CYP27B1) leads to the synthesis of the active metabolite – 1,25-dihydroxycholekalciferol. The alternative metabolic pathway of 25-hydroxycholekalciferol leads via hydroxylation in position 24 (the reaction is catalyzed by the vitamin D 24-hydroxylase – CYP24).

There are at least two reasons for setting the low end of the normal range of vitamin D levels at 30 ng/µl. First of all, it is suggested that serum concentration of vitamin D over 30 ng/µl guarantees optimal calcium absorption and below this concentration levels of parathyroid hormone (PTH) rise (Rosen, 2011). Secondly, this concentration provides an adequate amount of substrate for the nonrenal conversion of $25(OH)D_3$ to $1,25(OH)_2D_3$. It is assumed that children have the same requirements as adults, however no comparable studies have been carried out on intestinal calcium absorption and parthyroid hormone levels in children.
During last years vitamin D deficiency and insufficiency has been recognized as a 21st century pandemic and after changing the ranges of vitamin D concentrations defined as

normal, it is estimated that this problem concerns as much as 30-50% (according to some sources up to 80%) of the general population (Hollick & Chen, 2008, Ovesen et al., 2003). In a Euronut-Seneca study that compared vitamin D status in elderly citizens in Europe living in latitudes from 35^0 to more than 60^0 the mean $25(OH)D_3$ concentrations ranged from 20 to 60 nmol/l and surprisingly, were higher in the northern countries than in the Mediterranean area (Wielen et al., 1995). This data was confirmed by the results of MORE study conducted in women with osteoporosis (Lips, 2010). In Middle East and in India, vitamin D status correlates with clothing style and is believed to be the lowest among all continents (Arya et al., 2004, Sachan et al., 2005). In South East Asia vitamin D status is generally better (Fraser, 2004). In studies performed in North America several ethnic and life-style related differences in vitamin D status were observed. However, in general, vitamin D deficiency was higher in non-hispanic whites compared to non-hispanic blacks and was in between in Mexican-American (Looker et al., 2008). In Africa, it was reported that the vitamin D status improves from north to south (Prentice et al., 2009) whereas in Australia and Oceania, the trend is opposite (Rockell et al., 2006).

Although studies performed in different continents cannot be exactly compared due to e.g. (i) different methods used to asses $25(OH)D_3$ concentrations (precision and accuracy may vary depending on the kind of the assay) (ii) seasonal fluctuations in the vitamin D dietary intake (iii) seasonal variations in efficacy of cholekalciferol skin synthesis (it is estimated that in northern latitudes serum $25(OH)D_3$ levels decline from late summer to midwinter by 20%), some general patterns suggested by these studies can be recognized. In adults, groups at the highest risk of vitamin D deficiency are elderly (especially those in nursing homes) and obese subjects, and those who due to religious habits are wearing clothes covering most of the body (Lips, 2010).

Based on epidemiological studies it is estimated that an average dietary intake of cholecalciferol is as small as only 200 IU per day, thus the main source of vitamin D remains its skin-derived synthesis that covers as much as 90% of body's total requirements. However it should be emphasized that its efficiency is highly variable and anything that hampers transmission of solar UVB radiation to the earth surface and anything that diminishes the penetration of UVB radiation into the skin will affect efficacy of vitamin D skin synthesis.

Since melanin is extremely efficient in absorbing UVB radiation, individuals with increased skin pigmentation have reduced abilities of vitamin D skin synthesis and are at higher risk of vitamin D deficiency. Appropriate application of sunscreens results in the similar effect. The angle at which the sun reaches the earth has a significant effect on the number of UVB photons that reach the earth surface therefore geographic latitude and season (autumn and winter) as well as agegeographic latitude and season (autumn and winter) as well as age (elderly people have 75% lower concentrations of vitamin D precursor 7-dehydrocholesterol), sex (vitamin D status is usually lower in women) and cultural conditionings (especially practice of purdah that totally prevents exposition of the body to sunlight) are another factors potentially reducing efficacy of vitamin D skin synthesis (Webb, 2006).

Apart from UVB-related vitamin D deficiency, there are several medical or physical conditions which may impair vitamin D status, that include, among others: fat malabsorption, use of anticonvulsant drugs that induce catabolism of vitamin D active metabolites, chronic kidney disease or obesity (fat tissue is known to entrap vitamin D) (Zhang & Naughton, 2010).

Recently the scientists focused their attention on the problem of air pollution as an important factor reducing the amount of UVB radiation reaching the earth surface and therefore correlating with prevalence of vitamin D deficiency.

4. Correlation of air pollution and prevalence of vitamin D deficiency, insufficiency and adequacy

Air pollution is regarded as a dominant factor influencing the extent of solar UVB reaching earth surface. It was proved by both: observational and prospective studies, performed in different populations living in different geographic latitudes that atmospheric pollution (especially high tropospheric ozone content) may play a significant independent role in the development of vitamin D deficiency. Tropospheric ozone can efficiently absorb UVB radiation and decrease the amount of photons reaching ground level. It was proved that the level of air pollution is inversely related to the extent of solar UVB that reaches earth surface. Since industrial areas are those, of the highest intensity of air pollution, prevalence of D hypovitaminosis among urban residents can be more than twice higher compared to rural inhabitants.

To date, there have been published only 3 studies that attempted to correlate the intensity of air pollution with the prevalence of vitamin D deficiency, however their results are unequivocal.

In the tropics, children who live in regions with higher levels of ambient air pollution have been shown to be at increased risk of developing vitamin D-dependent rickets, compared to those living in less polluted areas (Agarwal et al., 2002). Children living in the highly polluted part of Delhi, despite similar types of housing, had significantly lower mean serum concentrations of $25(OH)D_3$ compared to those living in the less polluted areas of the city. The prevalence of vitamin D deficiency was correlated with the intensity of air pollution that in turn correlated inversely with the amount of UVB light reaching the ground level. None of the children included into the study used any vitamin D supplementation or consumed vitamin D fortified food, so the differences in the vitamin D status of the children cannot be explained by different dietary habits. However the authors did not collect data regarding time which each of individuals spent on exposition to sunlight that seems to be a chief limitation of this work.

In another study performed in adult European citizens of urban areas above 35^0 N (where cutaneous vitamin D synthesis in winter is nearly negligible), prevalence of vitamin D insufficiency was significantly higher compared to rural residents (38% *vs* 18%) (Manicourt & Devogealer, 2008). The compared groups did not differ in the mean age, body mass index and amount of time spent outdoor. Therefore the authors concluded that the observed difference in vitamin D status must be due to the efficacy of vitamin D cutaneous synthesis. The main reason of this phenomenon was 3 times higher tropospheric ozone concentration in urban compared to rural areas. These results were confirmed by a subsequent study performed in urban and rural areas of Iran (Hosseinpanah et al., 2010), where air pollution (determined as the high tropospheric ozone content) was found to be an independent, significant risk factor of vitamin D deficiency.

For many years the problem of vitamin D insufficiency has been underestimated, associated only with calcium/phosphorus metabolism and regarded as an area of interest reserved only for pediatricians or orthopedists. However, the last years brought a number of

epidemiological studies revealing the unexpected connection between the vitamin D hypovitaminosis and prevalence of several diseases that have forced the scientist to revise their opinions on the mechanism of vitamin D action and its role in the maintenance of body homeostasis (Walters, 1992).

5. Vitamin D mechanisms of action

$1,25(OH)_2D_3$ may act in target tissues via both genomic and non-genomic mechanisms. The non-genomic mechanism which is still not fully understood, is associated with stimulation of the enzymatic activity of a nonreceptor protein tyrosine kinase Src that results in activation of the mitogen activated protein kinase (MAP) signaling pathway (Gniadecki, 1998). Much more is known about the interaction of $1,25(OH)_2D_3$ with its nuclear receptor VDR (vitamin D receptor).

VDR together with thyroid hormone receptor (TR) and retinoid-X receptor (RXR) belongs to the class II of nuclear receptors family that act as a transcription factors modulating expression of vitamin D-directed genes. Upon binding with $1,25(OH)_2D_3$, the VDR forms a heterodimer with the retinoid-X receptor and translocates from cytoplasm to nucleus where it interacts with vitamin D responsive elements (VDRE) in promoter regions of target genes and regulates their expression (Dusso & Brown, 1998) [Figure 2].

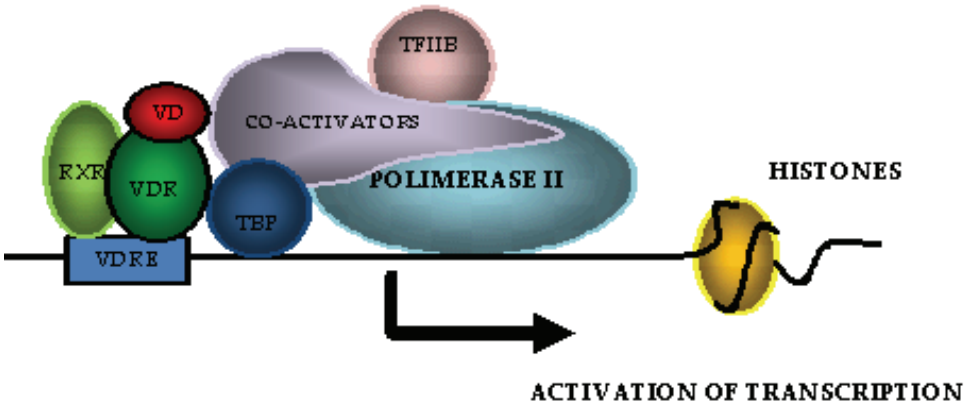

Fig. 2. The simplified scheme of activation of the target gene by the vitamin D receptor. The vitamin D receptor (VDR) with vitamin D (VD) binds as a heterodimer with the retinoid X receptor (RXR) specific sequence in the promoter region of the target gene – the vitamin D responsive element (VDRE). *Via* TATA binding protein (TBP) transcription factor II B (TFIIB), VDR gets in touch with the RNA II polymerase and other transcription factors (not present on these scheme). The transcription level is regulated by the complex of co-activators which bind VDR.

Identification of VDR in the intestine, kidney, bones and parathyroid glands (organs traditionally associated with mineral homeostasis) was not surprising. It is an undisputable fact that vitamin D is essential for maintenance of calcium and phosphorus homeostasis. In response to hypocalcemia-induced secretion of parathyroid hormone, and subsequent increase of *CYP27B1* expression and conversion of $25(OH)D_3$ to an active $1,25(OH)_2D_3$,

calcitriol, secreted to circulation, reaches the target cells and, after binding with VDR interacts with VDR-responsive elements in target genes that results in increased calcium and phosphate absorption in gut and in release of calcium and phosphate from the mineral phase of bones. Other actions of vitamin D related to bone metabolism include: inhibition of type 1 collagen synthesis, induction of osteocalcine production, stimulation of monocytes-macrophages differentiation into osteoclasts and production of RANK ligand which mediates in maturation of osteoclast precursors into osteoclasts, responsible for calcium mobilization from bones (Clarke & Kohsla, 2010).

The identification of VDR expression as well as the demonstration of the vitamin D 1α-hydroxylaze (CYP27B1) activity in a wide number of tissues other than bones (including, e.g.: skin, blood cells, prostate, breast, brain and skeletal muscles) started a new era in the understanding of vitamin D action and led to the designation of novel, so-called "non-calcemic" actions of calcitriol.

Nowadays, $1,25(OH)_2D_3$ can be defined as both a hormone (when it is synthesized in kidneys and secreted to the circulation) and as a cytokine. As a cytokine calcitriol participates in the regulation of innate immunity. It is synthesized locally by monocytes-macrophages and in an intracrine manner, *via* interaction with VDR, modulates immune response towards microbial agents. *In vitro* studies suggest also crucial role of $1,25(OH)_2D_3$ in regulation of differentiation, maturation and function of other antigen presenting cells – dendritic cells. Other functions of vitamin D in the immune system include: regulation of the differentiation and activation of CD4 lymphocytes, increase in the number and function of regulatory T cells (Treg) , reduction in the production Th1-derived cytokines, stimulation of the Th2 helper and natural killer (NK) T cells and probably many others (Marques et al., 2010].

$1,25(OH)_2D_3$ has been also shown to have antiproliferative and antiapoptotic properties. Although the exact mechanism by which $1,25(OH)_2D_3$ regulates cellular proliferation is not fully understood and may differ between tissues and cell lines, several pathways have been proposed. In *in vitro* studies, $1,25(OH)_2D_3$ *via* interaction with VDR, increases expression of cyclin-dependant kinase (CDK) inhibitors – e.g.: proteins p21 and p27. It results in keeping the cell in G1/S phase and in prevention of DNA synthesis (see Figure 3) as it was shown in experiments performed on human prostate adenocarcinoma (lymph node, carcinoma, prostate – LNCaP) and on human leukemia U937 cell lines (Zhuang & Burnstein, 1998; Liu et al., 1996). The inhibition of mitogenic signals transmitted via e.g. epithelial growth factor (EGF) receptor, inhibition of prostaglandins, activation of transforming growth factor β (TGF-β) and proteins binding insulin-like growth factor (IGF-BP3) are examples of other (and not only) mechanisms by which vitamin D is able to regulate cell cycle progression (Desprez et al., 1991, Moreno et al., 2006).

Apoptosis is an example of another cellular process which can be regulated by $1,25(OH)_2D_3$, however the exact mechanisms of this phenomenon are still being investigated. Experiments conducted on human breast cancer and on chronic lymphatic leukemia cell lines revealed that $1,25(OH)_2D_3$ is able to inhibit expression of the protooncogen *bcl-2* and increase expression of the pro-apoptotic protein Bax (Elstner et al., 1995, Xu et al., 1993). In addition, in breast and prostate cancers cell lines, calcitriol was shown to induce release of cytochrome c in the mechanism that does not depend on kaspases (Spina et al., 2006).

Apart from its engagement in cell proliferation and apoptosis, vitamin D has been also found to be involved in the regulation of cell adhesion and angiogenesis, two other processes important for cancer development and progression. "Anti-invasive" properties of

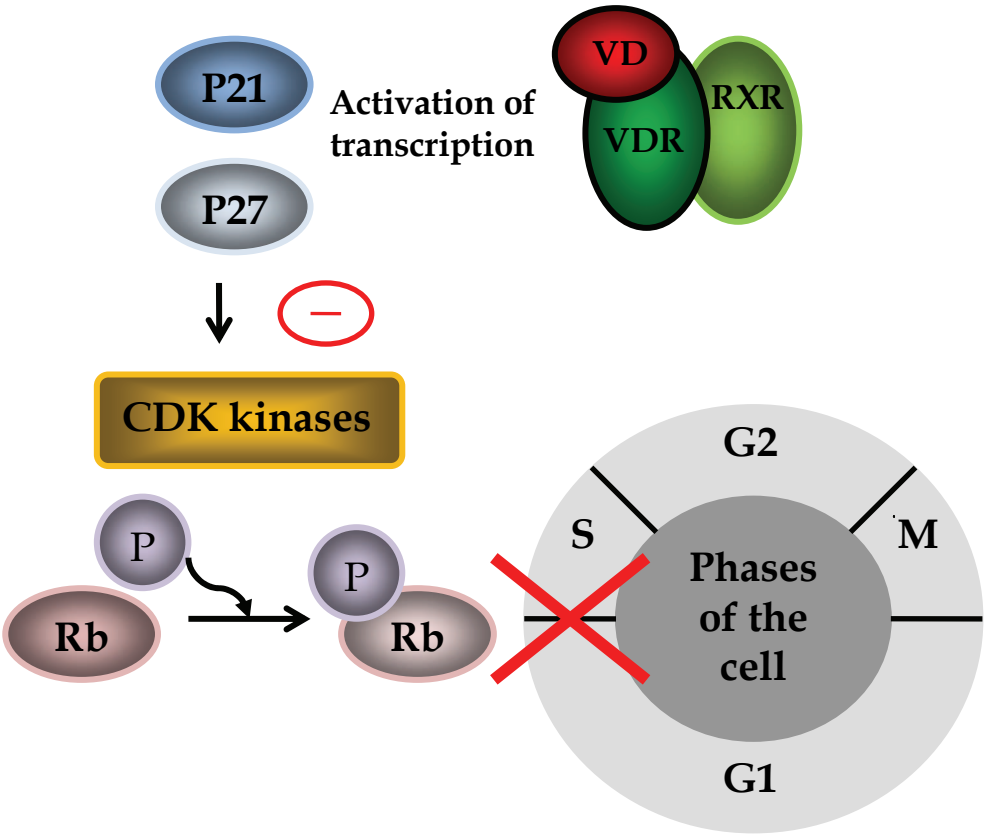

Fig. 3. Inhibition of cell cycle progresion by vitamin D
One of the factors determining the switch between G1 and S phases of the cell cycle is retinoblastoma (Rb) protein phosphorylation that leads to the release of several transcription factors activating genes involved in the cell cycle progression. Rb phosphorylation is catalyzed by the G1 cyclines and cyclin dependent kinases – CDKs. The CDKs activity can be inhibited by the p21 and p27 proteins. Vitamin D with the vitamin D receptor (VDR) binds to the regulatory sequences in the promoters of *p21* and *p27* genes activating their transcription that leads to the inhibition of the CDKs, lack of Rb phosphorylation and inhibition of the cell cycle progression.

$1,25(OH)_2D_3$ has been shown both in *in vitro* experiments (performed on human breast and lung cancer cell lines) as well as on animal models of prostate and bladder cancers, and include:

i. inhibition of metalloproteinases and serine proteases,
ii. up-regulation of cadherin E expression,
iii. down-regulation of integrin α6 and β4 expression (Bao, et al., 2006a, Hansen et al., 1994, Konety et al., 2001).

Inhibition of interleukin 8 gene expression (*via* interaction of $1,25(OH)_2D_3$ with p65 subunit of nuclear factor κB) is proposed as one of potential mechanisms by which calcitriol may interfere with the process of angiogenesis (Bao, et al., 2006b).
Knowledge of novel, non-calcemic actions of vitamin D that were proved in studies *in vitro* and on animal models, helps to understand the connection between the vitamin D and several human diseases that was reported by epidemiological studies.

6. Expected and unexpected consequences of vitamin D deficiency

Knowledge of traditional and novel, non-calcemic actions of vitamin D that were proved in studies *in vitro* and on animal models, helps to understand the connection between the vitamin D and several human diseases which was reported by epidemiological studies.

6.1 Musculoskeletal symptoms

For years vitamin D deficiency deficiency has been predominantly associated with impaired bone mineralization and development of rickets in children as well as osteopenia, osteoporosis and fractures in adults.
The consequences of vitamin D deficiency in mothers can be observed in the fetal skeleton just at the beginning of the 19th week of human gestation, resulting in rachitic phenotype, the severity of which is directly associated with a decreasing $25(OH)D_3$ level in the maternal circulation (Mahon et al., 2009). Vitamin D levels in infants correlate with vitamin D levels in their mothers during the first two months of life. Later, vitamin D status in babies, like in adults, depends on their diet and exposure to sunlight.
In rickets caused by vitamin D deficiency (a leading cause of rickets), both intestinal calcium absorption and renal phosphate reabsorption are significantly reduced. The decreased levels of serum calcium and phosphorus levels result in decreased bone mineralization. In addition, phosphorus deficiency contributes to the failure of the expected apoptosis of hypertrophic chondrocytes that results in deorganization of the growth plate. Clinical presentation of nutritional rickets depends on the duration and severity of vitamin D deficiency. At the beginning hypocalcemic symptoms are predominant, whereas skeletal deformities become obvious in later, more advanced stages. Classical symptoms of so-called "blooming" rickets include: craniotabes in infants older than 2-3 months, delayed fontanel closure, wrists enlargement, rachitic rosary, delayed teething, carious teeth, enamel hypoplasia, "O"- or "X"-type leg deforminty, kyphosis and narrow pelvis, chest deformities, costal or lower extremity fractures, caput quadratum, frontal bossing, fractures, brown tumor and extremity pain. Extra-skeletal symptoms include: hypotonia, constipation, proximal myopathy, cardiomyopathy and heart failure, myelofibrosis and pancytopenia, growth retardation, hypocalcemic convultions and benign intracranial hypertension (Levine, 2009).
Although full-symptomatic rickets seems to be nowadays a curiosity, epidemiological data indicate that rickets is not a disease of the past, nor it is limited to developing countries. It is estimated that nowadays 5 per 1,000,000 children aged between 6 months and 5 years have rickets, and the main risk factors for its development are breastfeeding and dark carnation. The peak prevalence of vitamin D-deficient rickets is characteristically between 6 and 18 months of age, with a further smaller peak occurring during adolescence (Nield et al., 2006).
In adults vitamin D deficiency can also cause a skeletal mineralization defect, resulting in osteomalacia demonstrating with isolated or global bone discomfort accompanied by joints

and muscle pain. However some observational studies conducted in adults and concerning the association between skeletal health and 25(OH)D_3 serum levels had conflicting results, suggesting both a strong correlation with the incidence of fractures and falls or only a fair relation (Chung et al., 2009). In general, it is assumed that the decrease of serum 25(OH)D_3 concentration that results in the persistent secondary parathyroidism enhances osteoclastogenesis and subsequent bone resorption.

The critical role of vitamin D in bone mineralization is well established, but our growing knowledge about non-calcemic actions of calcitriol led to the elongation of the list of diseases and conditions which development and/or progression can be associated with inadequate vitamin D status, including: different types of cancers, autoimmune disorders, cardiovascular events and probably many others. Interestingly, prevalence of this diseases frequently correlates with intensity of environmental pollution and many of them are diagnosed more frequently in inhabitants of industrial districts compared to rural areas (Pope, 2002, Pope, 2003, Grant, 2006, Ritz, 2010).

6.2 Vitamin D deficiency and cancer risk

The observational study conducted in 1941 reported that living at higher latitudes (where vitamin D skin synthesis is impaired) is associated with an increased risk of the development and dying of many common cancers including colon, prostate, ovarian and breast cancers (Apperly, 1941).

This observation was followed by the epidemiological studies performed in Europe and in the North America, assessing influence of many potential risk factors for incidence of cancers (e.g. smoking, alcohol consumption, economic burdens and environmental pollution) revealing that morbidity of several cancers (including colon, gastric, lung and breast carcinomas) is inversely associated with exposition to UVB radiation (Grant, 2003, Grant, 2005, Grant & Garland, 2006, Grant, 2009).

Next, on the one hand, another epidemiological prospective, study proved that vitamin D insufficiency (25(OH)D_3 concentrations below 20ng/ml) is associated with 30-50% higher risk of colorectal cancers (Garland et al., 2009). On the other hand, it was shown in a meta-analysis that appropriate (>400 IU) or increased (>1000 IU) vitamin D intake may be associated with a decreased risk of colon, breast, pancreas, esophagus and non-Hodgkin lymphomas (Garland et al., 2006, Giovannucci et al., 2006, Holick & Chen, 2008). It is estimated that the daily intake of 2000 IU of vitamin D would lead to 25% reduction in incidence of breast cancer and 27% reduction in incidence of colorectal cancer (Garland, 2009). Association of vitamin D deficiency with prevalence of breast, skin and prostate carcinomas has been also reported, however the concentrations at which the increased risk has been observed varied. Moreover, there are studies suggesting a U-shaped association between vitamin D concentration and cancers risk, pointing that some individuals may be adversely affected by elevated 25(OH)D_3 concentrations with respect to risk of prostate, breast, pancreas and esophagus cancers (Toner et al., 2010). This inconsistency may be caused by inadequate consideration of modifiers of 25(OH)D_3 concentrations. Therefore, to date, there is not yet sufficient evidence to recommend high-dose vitamin D supplementation for the prevention of cancer.

The hypothesis, about the connection between the vitamin D deficiency and cancer development, based on the observational data, has been confirmed by the *in vitro* studies described in the previous section and by experiments on animal models. For example: in vitamin D deficient Balb/c mice, injected with MC-26 colon cancer cells, the tumor growth

was accelerated, compared to vitamin D sufficient animals. In addition, vitamin D sufficient animals presented higher intra-tumor expression of VDR and CYP27B1, which suggests possible autocrine/paracrine cell growth regulation by vitamin D (Tangpricha et al., 2005). In turn mice with *vdr* knock-out (mutation that eliminates genomic action of $1,25(OH)_2D_3$) have been found to be more susceptible to develop leukemias, breast and skin cancers under the influence of common carcinogens compared to wild-type animals (Welsh et al., 2004).
Discovery of anti-cancer properties of vitamin D (that has no antioxidant properties) required a modification of a classic two-hit model of cancerogenesis, that provides that development of cancer depends on both: activation of proto-oncogenes and deactivation of tumor suppressing genes. Therefore, in context of vitamin D, a novel model of cancer pathogenesis has been proposed – a so-called: the Disjunction-Initiation-Natural Selection-Metastasis-Involution-Transition (DINO-MIT) model. This model is based on the classical concepts of carcinogenesis like initiation and promotion, however it includes also the life cycle of malignancies and provides an explanation of the ability of vitamin D to prevent or arrest the development of cancer (described in detail by Garland et al., 2006).

6.3 Vitamin D deficiency and autoimmune disorders

Similarly to carcinomas, prevalence of some autoimmune disorders such as multiple sclerosis and type 1 diabetes mellitus also correlates with the geographical latitudes. It has been proposed that vitamin D deficiency can disturb the immunological equilibrium and therefore contribute to the development of autoimmunity (e.g. by exacerbation of Th1 immune response) (Cantorna, 2004). In order to understand the complexity of these mechanism, again, insights from animal models of common human autoimmune diseases occurred to be particularly helpful.
Vitamin D deprivation leads to the acceleration of the development of experimental allergic encephalomyelitis (EAE – an animal model of multiple sclerosis) in mice immunized with myelin antigens (e.g. MOG35-55) (Cantorna et al., 1996). In turn, supplementation with active vitamin D metabolite and its analogs may favorably influence the course of autoimmune diseases or even prevent their occurrence. In mice immunization with type 2 collagen leads to the development of collagen induced arthritis (CIA – an animal model of rheumatoid arthritis), however, if the animals are given $1,25(OH)_2D_3$ till the 14^{th} day after immunization, they do not present any symptoms of arthritis at all. If $1,25(OH)_2D_3$ is given to mice with symptomatic artritis, it may alleviate the disease course (Cantorna et al., 1998). Similar evidence comes from the studies performed in nonobese diabetic (NOD) mice that due to the autoimmune inflammation and destruction of pancreatic islets develop insulin-dependent type 1 diabetes. In young subjects, administration of $1,25(OH)_2D_3$ till the third week after birth may completely prevent development of diabetes whereas in mature mice leads to the 50% reduction of inflammatory infiltrates in the pancreatic islets, compared with placebo-treated animals (Gregori et al., 2002). Reduction of T cells infiltration and decrease in the number of demyelinization sites has been also found in spinal cords of mice with experimental allergic encephalomyelitis treated with vitamin D analogs, compared to wild type animals (Mattner et al., 2000).
In humans, epidemiological data revealed that multiple sclerosis morbidity in Caucasians is significantly higher in less insolated areas, and the course of disease correlates with seasonal fluctuation of $25(OH)D_3$ serum concentrations (exacerbations in spring when $25(OH)D_3$ concentrations are the lowest) (Cantorna, 2008). Similarly, in patients with systemic lupus

erythematosus (SLE) severe vitamin D deficiency has been reported by many authors, and it correlates with disease activity (Kamen, 2010).
In contrary, like in epidemiological studies performed in different cancers, adequate consumption of cholecalciferol (400 IU per day) was shown, in a prospective study, to decrease a risk of multiple sclerosis development (relative risk – RR 0.59) (Munger et al., 2004). Vitamin D deficiency during the first year of life was found also to be a severe risk factor of type 1 diabetes whereas its proper administration in early childhood may reduce the risk of the development of this disease by 78% (RR 0.12) (Hypponen et al., 2001). A correlation between the adequate vitamin D intake and lower risk of the development of rheumatoid arthrits (RR=0.67) was reported (Merlino et al., 2004), however it was not confirmed by further studies [Costenbader, 2008]. Inconsistent are also results of the studies regarding the association between vitamin D intake during pregnancy and risk of type 1 diabetes in the offspring as well as with prevalence of other autoimmune disorders.
These discrepancies may be owed to the fact that, like in carcinogenesis, vitamin D deficiency is probably not the chief trigger in the development of autoimmunity. This hypothesis is supported by the *in vivo* experiments, where animals with vitamin D deficiency or with the knock-out of *vdr* gene do not present autoimmune disorders spontaneously and require other stimuli to develop autoimmunity. However these animals may present more severe disease phenotype of autoimmune disorders, as it was shown in mice depleted with IL-10 gene (animal model of inflammatory bowel diseases – IBD) (Froicu & Cantorna, 2007).

6.4 Vitamin D deficiency and cardiovascular health

Cardiovascular diseases are the most common cause of mortality and morbidity worldwide. There is also a growing number of evidence that vitamin D deficiency can be associated with development of several cardiovascular diseases including hypertension, ischemic heart disease and cardiac hypertrophy.
In vitro studies revealed that addition of $1,25(OH)_2D_3$ to the cardiomyocyte cells culture resulted in: inhibition of cell proliferation, enhanced cardiomyocyte formation, decrease of apoptosis and cell-cycle associated genes' expression. In turn animals with *vdr* gene knock-out were shown to develop cardiac hypertrophy, display hypertension as well as increased serum angiotensin and tissue renin levels. These studies suggest that vitamin D *via* its influence on cardiac and vascular structure and function may modulate cardiovascular risk (Artaza et al., 2009).
Observational studies reported a strong association between vitamin D hypovitaminosis and other traditional cardiovascular risk factors. Moreover, according to other reports, vitamin D deficiency is a predictor of all-cause and cardiovascular mortality, whereas vitamin D adequacy is associated with 43% reduction in cardiometabolic disorders (Parker et al., 2010).
The importance of vitamin D status in context of coronary artery disease is well established based on observational studies that reported:

i. inverse correlation of mortality from ischemic heart disease and the exposure to sunlight (Fleck, 1989),
ii. high prevalence of vitamin D deficiency in patients with ischemic heart disease (Kendrick et al., 2009),

iii. increased risk of sudden cardiac death, heart failure and fatal stroke in patients with ischemic heart disease who were vitamin D deficient (Pilz et al., 2008).

A correlation between the time of exposition to UVB radiation and decrease in blood pressure was also observed (Krause et al., 1998) and vitamin D replacement in deficient subjects led to a significant improvement of flow-mediated dilatation of the brachial artery that suggested an influence of vitamin D on vascular smooth cells (Tarcin et al., 2009). Indeed, it was shown on animal models that active vitamin D metabolite inhibits rennin expression in the juxtaglomerular apparatus and may prevent proliferation of vascular smooth muscle cells (Li et al., 2002; Carthy et al., 1989). Both, small retrospective observational studies and a large, cross-sectional study, confirmed that the mean blood pressure vary inversely with serum $25(OH)D_3$ concentrations and the association remained significant after adjustment for age, gender, race, ethnicity and physical activity (Scragg et al., 2007, Reddy Vanga et al., 2010).

Additionaly, individuals with vitamin D insufficiency have been found to higher prevalence of peripheral artery disease (Melamed et al., 2008) and worse outcomes in end-stage heart failure (Zittermann et al., 2008).

7. Vitamin D in treatment

Encouraging epidemiological data coming from observational studies, linking vitamin D deficiency with common human diseases, rose a hope that calcitriol and its derivates may be useful in everyday clinical practice (Holick, 2004, Holick, 2007). However, to date bone diseases are the only examples where administration of vitamin D is generally accepted for treatment.

7.1 Rickets and osteoporosis

In order to restore vitamin D reserve in rickets two methods of treatment are proposed. In a low dosage and long-term therapy model, vitamin D is administered 1000-10000 IU/day (dose depends on age) for 2-3 months. After that period 400 IU/day therapy is recommended to maintain the serum vitamin D level. Another regimen, reserved mainly for patients suspected of poor compliance, includes 100 000 - 600 000 IU of vitamin D in a single dose (Wharton & Bishop, 2003).

Prospective, randomized, placebo-controlled trials provided evidence supporting the benefit of vitamin D supplementation in patients with osteoporosis (LaCroix et al., 2009, Meier et al., 2004, Jackson et al., 2006). Data regarding a beneficial effect of calcium plus vitamin D on bone density in postmenopausal women and older men is consistent, however reports on fracture risk are more variable. Reduction in frequency of fractures was reported in some studies (Larsen et al., 2004) whereas large randomized trials have not shown any association between vitamin D supplementation and reduction in fracture risk. Additionally, in many of these trials, it is difficult to differentiate the effect of calcium from that of vitamin D. Nevertheless, in the Women's Health Initiative (the largest of the available trials) subgroup analysis revealed that calcium and vitamin D supplementation was associated with reduced fracture incidence in those subjects who were most compliant (Jackson et al., 2006).

Although the optimal serum concentration of $25(OH)D_3$ in patients with osteoporosis is not clear, based upon meta-analyses, one approach to vitamin D supplementation would be to give 400-800 IU daily with a target serum $25(OH)D_3$ concentration >20 ng/ml. Older

individuals with greater risk may require higher amounts that allow to maintain serum levels of $25(OH)D_3$ from 30 to 40 ng/ml (Dawson-Hughes, 2005). Yearly high-dose of vitamin D (e.g. 500,000 IU) for the osteoporosis treatment is not recommended.

7.2 Cancers

In observational studies, sufficient exposition to UVB radiation and vitamin D adequacy have been found to improve prognosis in cancer patients. A study assessing the survival rates for several cancers (including breast, colon, prostate, lung carcinomas and Hodgkin's lymphoma) revealed that patients diagnosed in autumn had approximately 30% higher 18-month survival rate than those diagnosed in winter or spring (Robsahm et al., 2004, Porojnicu et al, 2007).

Results of recent observational studies, reporting that maintenance of $25(OH)D_3$ levels about 30ng/ml may be crucial in the prevention of breast, colon and prostate carcinomas (Garland, 2009), together with newly discovered, proapoptotic and anti-proliferative properties of vitamin D stimulate hope that $1,25(OH)_2D_3$ and its analogues will have practical application in treatment of cancers. Severe hypercalcemia has occurred to be the chief limitation for the common use of vitamin D derivates in oncology and therefore vitamin D analogues are used mainly in combination with other anti-cancer drugs in reduced doses. Both *in vitro* and *in vivo* studies suggest that addition of vitamin D may potentializate action of many drugs commonly used in cancer treatment, including e.g: dexamethasone, docetaxel, paclitaxel, tamoxifen, retinoids, platinium derivatives and others (Gewirtz et.al., 2002). Administration of $1,25(OH)_2D_3$ may also sensitize cancer cells to radiotherapy as it was shown in prostate cancer line LNCaP or breast cancer line MCF-7 (Dunlap et al., 2003, Polar et al., 2003).

Numerous vitamin D analogs with minimal calcemic activity have been designed with intent to be applied in cancer therapy and some of them have been found to be effective in inhibiting tumor growth (e.g. colon) in animal models. Some of them are tested for treatment (e.g. calcipotriol administered locally in skin metastases of breast cancer) however to date, no active analogs of vitamin D have been proved to be efficacious for the treatment of any human cancer by themselves.

No prospective, randomized, double-blind study has been conducted in order to asses the anticancer potential of vitamin D analogues in humans. However, in a small pilot study performed in 7 patients with prostate cancer, daily administration of 0.5-2.5 μg/24h of $1,25(OH)_2D_3$ per 6 to 15 months, resulted in significant reduction of prostate specific antigen (PSA) concentration in 6 individuals (Gross et al., 1998). In another study, 37 patients with prostate cancer insensitive to androgens, were given sequentially 0.5 μg of $1,25(OH)_2D_3$ (day 1) and 36 mg/m^3 of docetaxel (day 2) during 6 following weeks and put on diet containing 400-500 mg of calcium per day. In 30 of them (81%) a significant reduction of PSA concentration was observed after 8 weeks from the beginning of the treatment (Beer et al., 2003).

7.3 Autoimmune diseases

Despite solid clinical and experimental evidence regarding the positive influence of vitamin D derivates on the development and progression of autoimmune disorders, to date vitamin D is not routinely administered in their treatment.

The only disease with partially autoimmune pathogenesis, where vitamin D and its analogs are generally accepted for the treatment is psoriasis. Both systemic and topical

administration of vitamin D and its analogs leads to the significant improvement in 70-80% of the treated patients, measured by the Total Severity Score (TSS) or Psoriasis Area Severity Index (PASI) (Ashcroft et al., 2000). Administration of vitamin D for treatment of other autoimmune diseases is still experimental since in humans only small and non-controlled studies have been conducted. For instance, in a an open study performed in 19 patients with rheumatoid arthritis, addition of alphacalcidol ($1\alpha(OH)D_3$) to the traditional disease-modifying anti-rheumatic drugs for three months, resulted in a significant reduction of symptoms in 89% of patients (45% achieved complete remission and 44% had satisfactory results) without side effects (Andjelkovic et al., 1999). There is also one report on a positive influence of $1,25(OH)_2D_3$ on thyroid hormones levels in patients with autoimmune hyperthyroidism, who acquired the treatment in order to improve bone mineral density (Kelman & Lane, 2005).

7.4 Cardiovascular health

To date, studies evaluating influence of vitamin D supplementation on cardiovascular health are few and have inconsistent results. Observational studies reported that individuals who take oral vitamin D supplementation have lower blood pressure and some interventional trials found a correlation between oral vitamin D administration or increased exposure to UVB and decrease of blood pressure. However, this phenomenon was not confirmed by a large prospective studies and a meta-analysis on prevalence of hypertension and vitamin D intake (Forman et al., 2005, Witham et al., 2009). Vitamin D supplementation seemed also to have no effect on the risk of cardiovascular mortality (La Croix et al., 2009).

8. Guidelines regarding vitamin D supplementation

The recognition of vitamin D deficiency as a worldwide problem rises a task of means of its supplementation. Historically, fortification of milk in the 1930s with vitamin D was effective in eradicating rickets in Europe and US. However, after an unexpected outbreak of hypercalcemia in British children in the 1950s caused by the excessive vitamin D consumption from fortified food, fortification of dairy products with vitamin D had been forbidden (Holick, 2010).This situation was probably caused by the imperfection of methods applied to assess the vitamin D concentration in food at that time.

Naturally the main source of vitamin D are wild-caught, not farm-raised oily fish, e.g. salmon, mackerel, herring, and oils from fish. However, since no quality control over vitamin D content in natural products is available, they are not recommended as reliable sources of vitamin D supplementation. In many countries dairy products, juices, bread and other products are fortified with vitamin D.

The recommendations of American Institute of Medicine from 1999 state that all children and adults up to the age of 50 should consume 200 IU of vitamin D daily, whereas individuals aged 51-70 and those who are over 71 years old, 400 IU and 600 IU, respectively. However, these amounts have been insufficient in prevention of osteomalacia and osteoporosis, and therefore many experts now suggest that, in the absence of the adequate sun exposure, as much as 800-1000 IU of vitamin D per day is needed for healthy individuals, regardless of age (Holick and Chen, 2008). In case of diseases leading to vitamin D mal-absorption or sequestration in fat tissue (obesity), higher doses may be required. In aspect of cancer prevention, the National Academy of Sciences-Institute of Medicine (USA)

recommends even 2000-4000 IU/day (Garland, 2009). It is estimated that raising the mean population level of $25(OH)D_3$ up to 42 ng/ml would result in 18% reduction in all-cause mortality, 25% reduction in prevalence of cancers and cardiovascular diseases, 15% in morbidity of diabetes and a prevalence of multiple sclerosis would be reduced by half (Grant & Schuitemaker, 2010), however approaching this vitamin D status would require supplementation of 2500-4000 IU of cholecalciferol per day.

According to the nutritional guidelines established during the 14th vitamin D workshop in October 2009, appropriate vitamin D status should be achieved rather through supplementation than diet fortification and rather through the use of vitamin D_3 than vitamin D_2. It is suggested that vitamin D_2 is in half less effective than vitamin D_3 in maintaining the $25(OH)D_3$ serum levels and therefore it should be administered in higher doses. Moreover, all evidence reported to date on the efficacy of vitamin D in e.g. cancer prevention has been based on vitamin D_3. To verify this theory, a number of prospective vitamin D replacement trials with vitamin D_2 and vitamin D_3 has been conducted (Adams & Hewison, 2010).

In the treatment of evident vitamin D deficiency 50 000 IU of vitamin D is recommended weekly for 8 weeks, resulting usually in $25(OH)D_3$ concentration of 30 ng/ml, and after 50 000 IU of vitamin D every 2 weeks to maintain its level. It has been estimated that for every 100 IU of vitamin D ingested, there is an increase in the blood level of $25(OH)D_3$ of 1 ng/ml and sensible exposure to sunlight is more effective in raising blood levels of $25(OH)D_3$ than 1000 IU vitamin D_3 taken daily for adults of most skin types. However, with the growing intensity of atmospheric pollution, which as it was shown above, is a chief factor limiting the amount of UVB radiation reaching the earth surface, obtaining appropriate amount of vitamin D from skin synthesis is getting more and more challenging.

9. Conclusions

Based on the available observational and experimental data regarding the connection between the air pollution, vitamin D status and related health consequences, following statements can be formulated:

i. the worldwide problem of vitamin D deficiency can be partially explained by the growing intensity of atmospheric pollution, however this observation is based only on the results of relatively small studies and should be replicated in larger scale,
ii. both: vitamin D deficiency and intensity of air pollution correlate with prevalence of common human diseases including different types of cancers, cardiovascular and autoimmune diseases that was confirmed by large, prospective studies and meta–analyses,
iii. association between vitamin D status and extra–skeletal health outcomes can be explained by the molecular mechanism of vitamin D action that exceed bone metabolism,
iv. despite promising results of *in vitro* and *in vivo* studies regarding the favourable influence of vitamin D supplementation on prevalence and course of different diseases, its therapeutic application is still limited only to the treatment of bone diseases,
v. novel definition of vitamin D insufficiency together with the increasing intensity of the atmospheric pollution that impairs vitamin D skin synthesis and with epidemiological data regarding the benefits of vitamin D intake should result soon in the novel guidelines regarding vitamin D supplementation.

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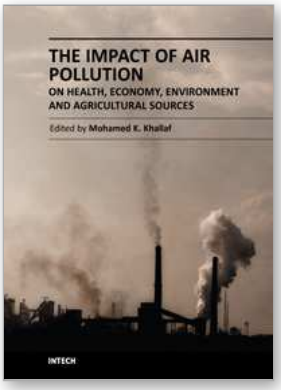

The Impact of Air Pollution on Health, Economy, Environment and Agricultural Sources

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This book aims to strengthen the knowledge base dealing with Air Pollution. The book consists of 21 chapters dealing with Air Pollution and its effects in the fields of Health, Environment, Economy and Agricultural Sources. It is divided into four sections. The first one deals with effect of air pollution on health and human body organs. The second section includes the Impact of air pollution on plants and agricultural sources and methods of resistance. The third section includes environmental changes, geographic and climatic conditions due to air pollution. The fourth section includes case studies concerning of the impact of air pollution in the economy and development goals, such as, indoor air pollution in México, indoor air pollution and millennium development goals in Bangladesh, epidemiologic and economic impact of natural gas on indoor air pollution in Colombia and economic growth and air pollution in Iran during development programs. In this book the authors explain the definition of air pollution, the most important pollutants and their different sources and effects on humans and various fields of life. The authors offer different solutions to the problems resulting from air pollution.

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