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Low levels of vitamin D in population exposed to significant pollution

Josef Richter[1], Vaclav Vetvicka[2], Stanislava Richterova[3]

(1. Usti nad Labem Zdravotni ústav se sídlem v Usti nad Labem, Usti nad Labem, Czech Republic; 2. Department of Pathology, University of Louisville, Louisville, KY, USA; 3. Usti nad Labem, Zdravotni pojistovna, Usti nad Labem, Czech Republic)

Contributions: (I) Conception and design: J Richter, S Richterova; (II) Administrative support: J Richter, S Richterova; (III) Provision of study material: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Abstract **Background:** In recent years, monitoring of vitamin D levels and possible use of supplementation is gaining attention. Numerous studies showed low levels of vitamin D in winter months followed by improvement during summer. These changes are mostly dependent on the level of sun exposure, but also on geographical location, genetic factors, social-economic status, quality of nutrition and environmental pollution. In this observation we found significant decrease in vitamin D levels I populations exposed to extreme environmental pollution in area of central Europe. This region is known for extreme burden from microparticles originating in chemical industry, surface coal mining and cold-based power stations. **Methods:** Vitamin D levels in all patients was determined by ELISA. **Results:** Using 540 patients in our Department of clinical immunology and allergology we measured the levels of vitamin D in 2016 to 2021 period. In only 4 patients (0.74%) we found vitamin D levels higher than 30 ng/mL. The curve of observed values does not reflect dependency on sun exposure and does not change during the year. **Conclusion:** We discuss the effect of environmental contaminants, lifestyle and economic and social factors. From our observations, we propose to directly supplement population with vitamin D, particularly children and seniors.

Keywords vitamin D; pollution; environment

Monitoring of vitamin D levels is recently gaining attention. Deficit or insufficiency of this vitamin was found world-wide[1-10]. New findings showing relation and importance of vitamin D for bone metabolism, calcium and phosphorus regulation and homeostasis increased the interest of both general public and medical professionals[3-4,11-12]. In addition, insufficient bone mineralization results in rachitis in children and osteomalacy in adults[4,6-7]. Last two decades found improved knowledge on pleiotropic and general effects of vitamin D on human health[4,6,13]. Numerous important studies revealed that vitamin D deficit results in higher risk of induction of several diseases. Good levels of vitamin D can reduce risk of many cancer diseases, metabolic problems, cardiac and autoimmune diseases, diabetes type 1 and 2 and some neuropsychologic problems[4,10,13-15]. Vitamin D deficit represents important etiologic factor in pathogenesis of numerous chronic diseases with significant increase of mortality[13,16]. All these findings resulted in conclusion that vitamin D can be considered to be pre-hormone induced by UVB spectrum at the 290–315 wavelength

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Corresponding author: Vaclav Vetvicka. Email: vaclav.vetvicka@louisville.edu

via 7-dehydrocholesterol present in the skin with subsequent hydrogenation in the liver by numerous enzymes. Levels of serum 25-hydroxy vitamin D [25-(OH)D3] reflect nutritional reserves of vitamin D. Another step in obtaining active vitamin D is 1-alpha-hydrolyzation (CYP P27D1). This enzyme is present mostly in proximal kidney tubulus, but can be also found in the skin, immune cells, placenta and bone cells. Activity of 1-alpha hydrolases is regulated by calcium and phosphates. The role of nutrition of saturation of vitamin D level is minimal and usually reaches about 8% of total values. Vitamin D and its metabolites are in circulation bound to multifunctional vitamin D-binding protein DBP, which in addition to transfer of vitamin D also modulates inflammatory immune response and regulates development of bones. The importance of vitamin D for regulation of both native and adaptive immunity was demonstrated by the presence of VDR expression on almost all cells involved in immune processes[17-19]. VDR of gut mucosa is important for defense of mucosal surfaces, maintaining of their integrity and regulation of native immunity[17-18,20]. Direct immunomodulatory effects of active vitamin D on T lymphocytes results in tolerance via induction of Th2 and regulatory lymphocytes and subsequent reduction of levels of Th17, Th9 and Th1ly lymphocytes. NK cells with VDR expression have upon D3 binding quite opposite effect, resulting in minimalization of pathogen-caused damage. Process of macrophage deactivation is associated with ORO1 protein[20]. Epidemiological studies suggested that vitamin D deficit results in a decrease of immune reactions with subsequent risk of development of infections and autoimmune diseases. Active role of vitamin D in immune reactions occurring during vaccination against flu (showed) additional possibilities of normal vitamin D levels in protection against viral diseases. Recent experimental and clinical findings support the necessity of detailed studies of relation between immune response and vitamin D. Actual stages of current COVID pandemic are not adequately reflected in studies of possible involvement of vitamin D. In our study, we focused on some aspects of this problem.

Vitamin D synthesis is influenced by geographical region, altitude, and intensity and length of sunshine. Another important factor is skin pigmentation (so called phototype), age, sex and genetics. Figure 1 shows significant differences between sunshine length in the selected region of Usti nad Labem (UL) and other regions such as Prague (P) and Rome (R). The differences are clear, despite the fact that in Prague and Rome regions the quality of sunshine is reduced by contaminations. Current trends in urbanization results in developments mimicking condition in London or Warsaw of the 19th century. In the UL region, the amount of sunshine is consistently low, mostly due to the extreme contamination of environment caused by heavy industry, mining and coal-based power stations. Exposure to organic compounds is several times heavier than in bordering German regions.

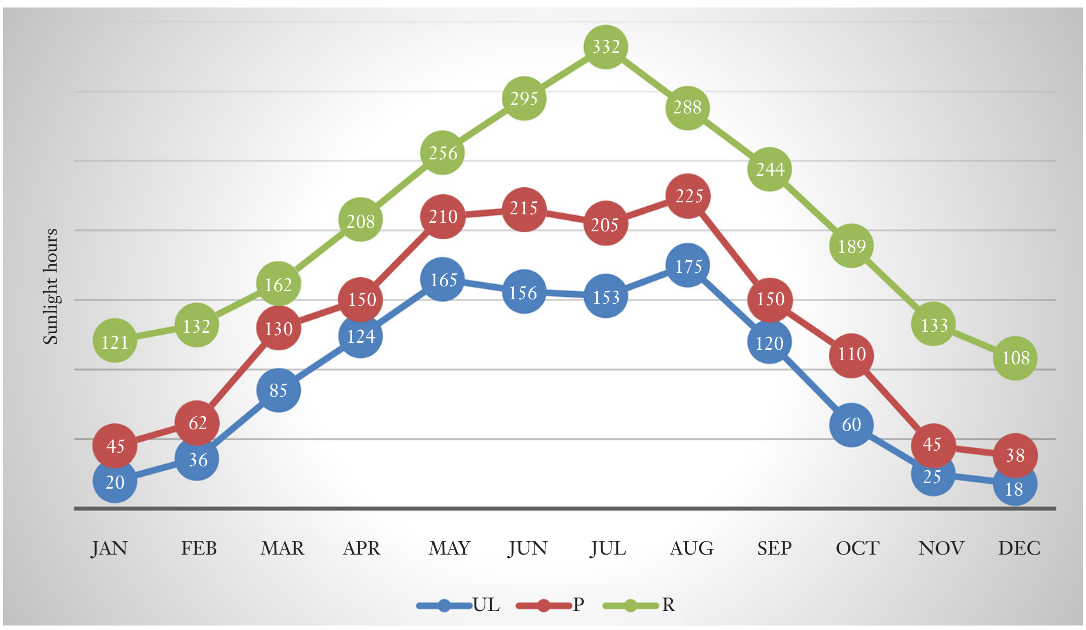

Figure 1 Sunshine in various locations—Usti nad labem (UL), Prague (P) and Rome (R) Individual values and given as h/month.

European population shows significant deficit in vitamin D. Individual countries do not significantly differ, despite differences in lifestyle, economy and location (Figure 2). Older studies performed in the Czech Republic showed similar data[6-8,10,21]. Specific conditions found in the UL region, which is sometimes called "European black spot" together with its low social-economic condition of the population led us to evaluate the levels of vitamin D in this region.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.3978/j.issn.2095-6959.2022.01.001).

1 Materials and Methods

We used 540 patients from our Department of Clinical Immunology and Alergology (Zdravotni ustav Usti nad Labem, Czech Republic) during the 2016–2021 period. During initial observation, we eliminated patients which used vitamin D supplementation. Among the 540 patients, 325 were females and 215 males, the age was 12 to 84 years. Initial diagnosis revealed repeated infections of the respiratory tract, chronic lung disease, bronchial asthma, allergy, particularly with the specific IgE response to inhaled allergens, and immunodeficits, particularly IgA deficit and IgG4 syndrome.

Vitamin D levels were determined by ELISA using kits and standards from DRG (DRG Instruments, Germany) according to the manufacturer's instruction.

We explained the experimental protocol and obtained consent forms from all participating patients. This study was Institutional Review Board approved and performed in full agreement with the Helsinki declaration (revised version 2000.09.01), and in full compliance with the Czech Republic's clinical testing rules.

Paired *t*-test statistical significance was evaluated (GraphPad Prism 5.04; GraphPad Software, USA). An average and standard deviation was evaluated after determining standard value composition (D'Agostino, Pearson). In case of nonstandard composition, values were converted into logarithms.

2 Results

The prevalence of vitamin D levels in tested population is shown in Figure 3. Cumulative deficit (below 10 ng/mL) was found in 3.52% of patients, insufficient levels (up to 20 ng/mL) in 45% of population and suboptimal levels in 99.26%. Only 4 patients (0.74% of tested sample) had vitamin D levels higher than 30 ng/mL. Figure 4 shows that there were no differences between males and females in individual age groups. The findings of changes in vitamin D levels during the year was surprising, as we found no typical changes based on season (Figure 5). The levels found in males and females here were statistically different (P=0.025).

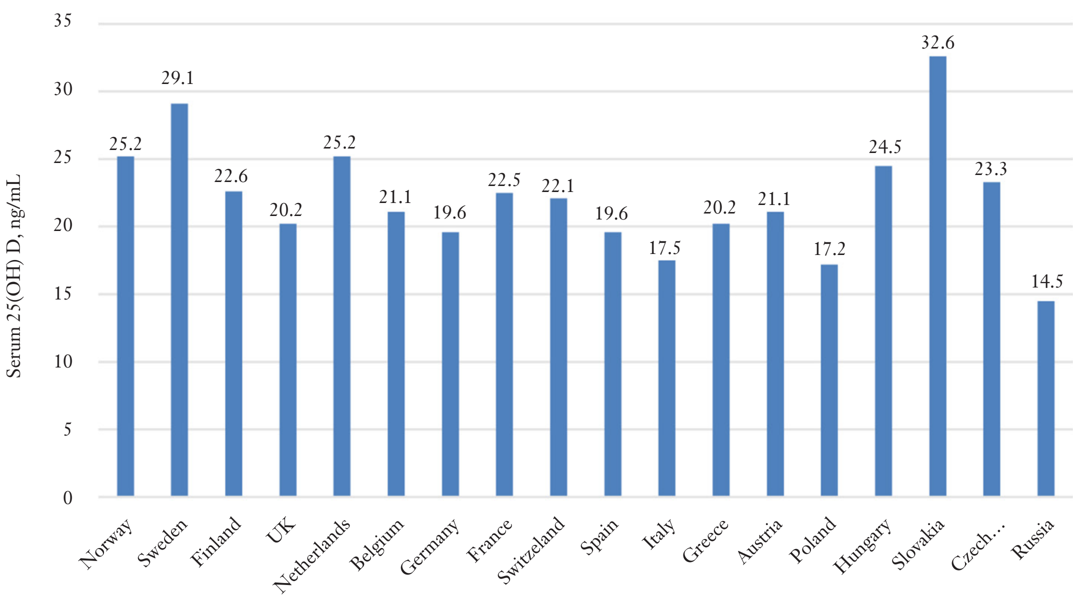

Figure 2 Levels of vitamin D in individual European countries. Data are shown as average serum levels (ng/mL).

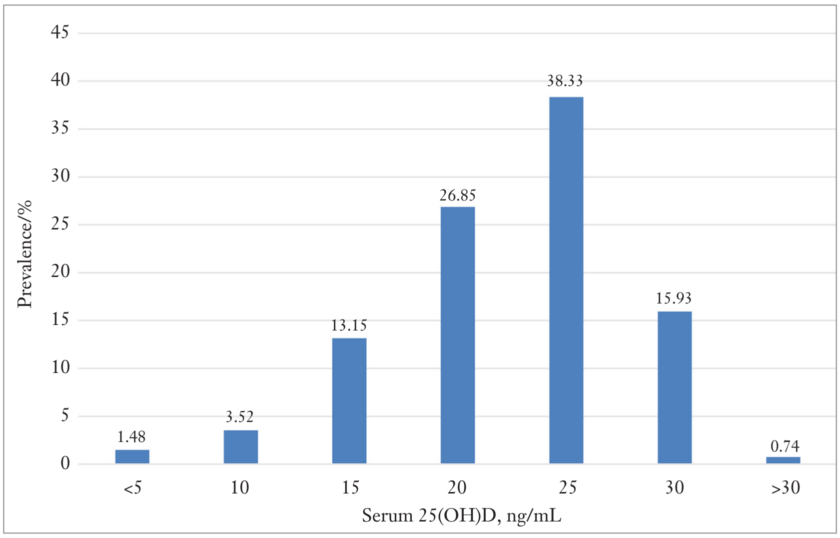

Figure 3 Prevalence of average values of vitamin D in Usti nad Labem region.

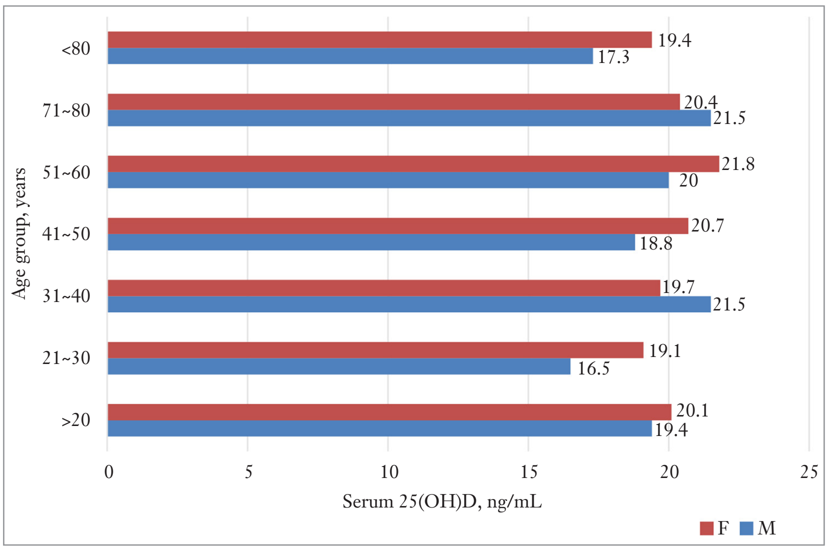

Figure 4 Average levels of vitamin D based on sex (males and females) and age categories.

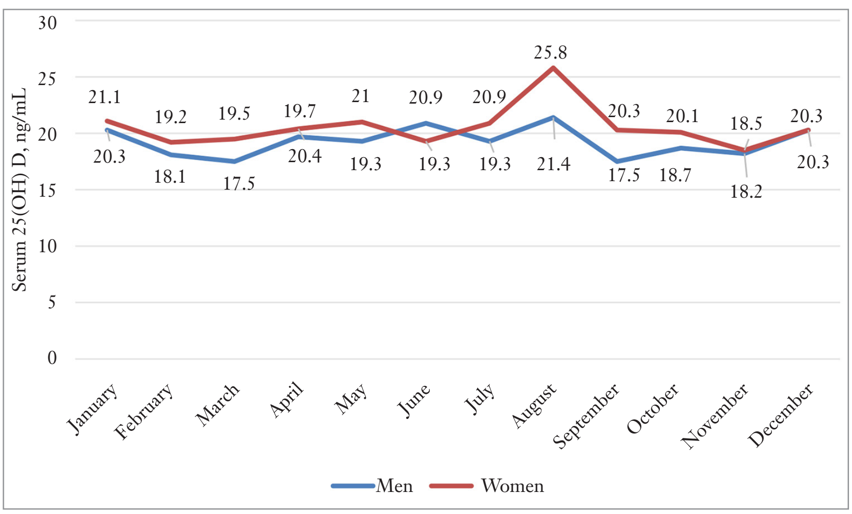

Figure 5 Average levels of vitamin D in serum of males and females in individual months.

3 Discussion

Sunshine can affect human health both negatively (risk of development of some types of cancer), and positively (most of all by induction of vitamin D production). A long-term damage might result in immunosuppression or sunstroke, long-term effects result in risk of skin aging, cataracts, and DNA damage with subsequent mutations and possible cancer development. Levels of 25(OH)D are affected by nutrition (app. 5–10% of total value) and sun exposure[4,8,10,13,21-23]. The synthesis of the biologically active 1,25-dyhydrovitamin D form is determined by numerous effects, including the location, altitude, length of exposure, age, sex, type of clothing and environmental pollution. Ecological studies suggested that urban development is similar in the whole developed world and results in significant impact on elimination of sunshine exposure[4]. High concentration of people in city centers is affecting the access to sunshine in all age populations[4,22,24]. Figure 1 clearly shows significant difference in sunshine in North Bohemia region (UL), capitol Prague (P) and theoretically optimal Rome (R). Year-long exposure in Rome is 2,468 h, in Prague only 1,585 h (65%) and in Usti nad Labem only 1,137 h (46%). In theory, the levels of 25(OH)D should correspond to these values. However, whereas levels found in Prague (22–25 ng/mL) are significantly different from levels in Usti[7], levels in Italy are similar to U[6-7]. Similar findings were found in other Middleterranean countries such as Spain or Greece. Comparing European countries (Figure 2), the differences in 25(OH)D levels in Northern Europe with significant supplementation program and vitamin D-high food and the rest of Europe is clear[25]. The strange levels found in Slovakia are currently hard to explain and deserve detailed study.

There are no doubts about the effects of sunshine on vitamin D production[25]. However, the intensity of sunshine in individual geographical and local situation is not fully understood. Comparison of time of sunshine during a single year in UL, P and R location should clearly show that vitamin D levels will be the highest in Italian population (Figure 2). However, some other factors must be involved. Environmental pollution by micro- and macroparticles reduces vitamin D production and recent studies demonstrate that this pollution is the main factor, regulating level of sunshine in the UVB spectrum and causing development of vitamin D deficit[11,26]. When bordering region of Germany and the Czech Republic were compared, the situation around Usti nad Labem (UL) was significantly worse[27]. We propose to add some more definition of the quality of environment by evaluating the level of UVB exposure[21]. Similarly strong effects on vitamin D deficit were found to be related to both active and passive smoking[28]. Based on these data, we propose nutritional changes at least in children[29]. Vitamin D supplementation is population exposed to pollution was found to improve the health problems caused by pollution[2], particularly in development of obesity, which is known to correlate with diet and environmental contamination[2,30].

Several mechanisms of low vitamin D levels and obesity development have been proposed. Besides nutritional factors and low physical activity, some studies suggested that a vitamin D deficit alone can result in obesity or at least in inhibition of losing weight[16]. Some of our tested patients, particularly those with higher phototype, bad nutritional habits and alcohol abuse can see results in suppression of PTH secretion and subsequent decrease of vitamin D conversion[23]. Increase of obesity development in older population might be another reason for low levels of vitamin D, where one can discuss possible effects of lover levels of leptin found in seniors[19]. In our patients we found low levels of leptin in group with high vitamin D deficit, diabetes and significant obesity. Reduction of antibody response to viral antigens can be another subsequence. One can assume that vitamin D supplementation would be optimal for lowering the effects of current pandemic, as is known that infection with COVID-19 results in pneumonia and additional complication[24]. In our clinic, no patient with repaired levels of vitamin D to the levels over 40 ng/mL was infected with COVID-19.

The question on which medication can affect vitamin D levels is gaining traction lately[3,4,31]. Besides drugs with direct interaction with vitamin D (such as rifampicin, cimetidine, corticosteroids and thyazides), drugs reducing absorption of vitamin D (such as orlistad or laxatives) similarly reduce the levels of vitamin D. Known increase in drug consumption observed in last decades deserves more attention with respect of potential interactions with vitamin D levels.

Our 6-year observation of effects of vitamin D supplementation used two to three regular yearly testing found part of the population, which is not, even with adequate doses of vitamin D, able to reach optimal level of at least 20–40 ng/mL. We presume that genetic disposition might play an important role in this aspect, and we suggest more detailed follow up study. It is important to note potential individual danger of low vitamin D levels resulting in development of cancer, autoimmune disease, bone problems and other illnesses[6,32]. From our observations we conclude that it is very difficult to suggest optimal vitamin D supplementation in this type of patients.

Another factor involved in low vitamin D levels is nutritional habit, particularly diet which is not consistent with recommended healthy diet. Steady decrease in fish consumption, often below 5 kg/person/year, often observed in our region, can often decrease the formation of active vitamin D. Lower level of social and/or economic situation makes this possibility even more probable. We agree with numerous authors that complex evaluation of lifestyle, nutrition and vitamin D levels is necessary to achieve better quality of life and improve the health of the population[15-16,33]. Supplementation of senior population seems to be a good approach to achieve these goals[23,25,34]. Prevention of vitamin D deficit should become priority of the health system, and it is even part of the project of the European Commission[35].

It is beyond doubts that vitamin D deficit is manifested by the damage of immune functions[17-18]. High frequency of immune system-related diseases such as multiple sclerosis, diabetes, autoimmune diseases, asthma and inflammatory diseases is more common in location which are further and further away from the equator. Similarly, different success of vaccination against flu, tuberculosis and other diseases is based on geographical location[17,19]. Vitamin D has become an important immunomodulator involved in numerous aspects of regulation of inflammatory response and mechanisms of all functions of both native and adaptive immune responses[9,17-18,20,24,27]. The importance of reaching optimal levels of vitamin D for induction of adequate antibody response to trivalent vaccination[19] suggests possible relation to the sensitivity of individuals with low vitamin D levels to COVID-19 infection[24]. Our experience suggest possible positive effects of vitamin D supplementation on reduction of risks involved in both infection and COVID-19 disease.

On the one hand, vitamin D cannot be considered a one-for-all type of drug. However, supplementation with this vitamin can be an easy, inexpensive and safe way how to medically improve various diseases, improve quality of life and even increase the lifespan[14,16,35].

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