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Vitamin D [25(OH)D] Deficiency Patients in Prostate Cancer in Latvia

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Authors' contributions

This work was carried out in collaboration between all authors. Author AS designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors OV and ZZ managed the analyses of the study. Author ZZ managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Nowadays the role of vitamin D is not only known to be limited to the maintenance of the bone health, but also to the reduction of the risk for development of many chronic diseases including autoimmune, cardiovascular, as well as various oncological diseases.

Aim of the work: To identify sources of vitamin D, as well as prevalence of vitamin D insufficiency and deficiency in aging men with the increased risk of prostate cancer.

Methods: The present case–control study included 252 respondents - men between 45-80 years of age, whose weight and height were measured, body mass index (BMI) was calculated, as well as both serum prostate specific antigen (PSA) and vitamin D (25 (OH) D) were determined. The study participants were divided into three groups: the first group consisted of men with PSA serum level <4.0 ng/mL, the second group with PSA >4.0-10.0 ng/mL, the third - PSA>10.0 ng/mL. We used the International Prostate Symptom Score *(*IPSS*)* to evaluate the symptoms, along with the physical examination (including a digital rectal exam or DRE). In the study group with reading of PSA> 4.0 ng/mL prostate biopsy was performed to determine the study participants with prostate cancer. Gleason score was used for the evaluation of prostate cancer malignity grade.

Statistical Analysis: The statistical processing of the obtained results was carried out by means of the parametric and non-parametric statistical methods. The statistical descriptive method also included the determination of the mean arithmetic mean (M), mean values (m), for normal symptoms. The t-test and variance analysis were used for the present study, and the relationship

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between two or more variables was found using linear correlation and regression methods. Pearson's correlation coefficient "*r*" test was calculated between PSA, IPSS and 25(OH)D, continuous variables. *P* <0.05 was considered statistically significant.

Results: 252 men were included in the present study, the mean age 59 ±7.9, the mean PSA level 4.3±0.42, BMI 28.4±0.25, IPSS 12±0.64, 25(OH)D 17.5±0.47. PSA <4.0, the mean 25(OH)D serum level was 19.95±6.87, PSA 4-10, 25(OH)D 14.31±7.43, PSA >10, 25(OH)D-11.46±3.50. However, the correlation between IPSS and Vitamin D using Pearson's correlation was statistically insignificant (*r* = 0.05 p<0.001).

Conclusions: Vitamin D deficiency and insufficiency are common in males with the increased risk of developing prostate cancer. The increase in PSA levels correlates with the lower vitamin D levels, as well as correlation between 25(OH)D serum level and increased prostate cancer risk was also found.

Keywords: PSA (Prostate Specific Antigen); vitamin D; 25(OH)D; IPSS (International Prostate Symptom Score).

1. INTRODUCTION

Nowadays the role of vitamin D is not only known to be limited to the maintenance of the bone health, but also to the reduction of the risk many chronic infections development including autoimmune, cardiovascular, as well as various oncological diseases.

The potential vitamin D anti - cancer activity both in the prostate cancer development and inhibition of a malignant disease progression was shown by some authors [1]. By means of the action of vitamin D receptors (VDR) - retinoid X and androgen receptors, vitamin D affects the prostate cancer cells by promoting differentiation and inhibiting both cell proliferation and metastatic spread [2,3]. The results of the epidemiological studies are rather inconsistent [4]. The potential vitamin D inhibitory effect on the prostate cancer was also studied in relation to its effect on prostate specific antigen (PSA) level. The data show that PSA rise in the prostate cancer patients is lower in the spring and summer months when vitamin D levels are higher [5], as well as some intervention studies demonstrate that vitamin D (Cholecalciferol) tends to lower PSA level in prostate cancer patients [6]. Some studies indicate a link between obesity and prostate cancer, and although the data is controversial, the relationship between increased body mass index (BMI) and PSA levels has been studied. Some studies are dominated by the data that overweight and obesity are associated with lower PSA levels, and the authors encourage to review the PSA "normal" levels in men with obesity, but this issue has not been proved yet [7,8]. BMI and PSA relationship is not entirely clear, it might be due to the metabolic and hormonal effects of the adipose tissue, as well as increased plasma volume, which produces a greater dilution of PSA in men with obesity [8]. The studies on the factors influencing the level of PSA have also shown a correlation between age and PSA levels [9].

1.1 Aim of the Work

To identify the sources of vitamin D; vitamin D insufficiency and deficiency prevalence in the aged men with increased prostate cancer risk.

Tasks:

1. To evaluate whether there is a relationship between the amount of vitamin D consumed and its serum level; vitamin D serum level and serum PSA, age, and BMI; to assess whether an increase in BMI is associated with lower PSA serum levels;
2. To make adjustments to the "food basket" of the existing "Food Consumption Frequency Questionnaire" in order to determine the intake of vitamin D;
3. By means of the BLS (Bundeslebens-mittelschlüssel) Max Rubner Institute German database:
    a) To determine the energy input and amount of basic nutrients;
    b) To analyze the "Food Consumption Frequency Questionnaire" to identify the major sources of vitamin D in the diet, as well as the total intake of vitamin D in the diet;
4. To determine the vitamin D serum level in men with prostate cancer;
5. To determine PSA serum level in men with prostate cancer.

2. MATERIALS AND METHODS

There were 252 respondents aged 45-80 years, the study took place from October, 2012 to December, 2016 at the Rehabilitation Center "Dzintarkrasts", Riga Health Center "Pļavnieki", Riga Eastern Clinical University Hospital, Latvian Oncology Center, Urology Department. Weight and height of the respondents were measured, body mass index (BMI) was calculated, as well as serum prostate specific antigen (PSA) and vitamin D (25 (OH) D) were determined. The study participants were divided into three groups: the first group consisted of men with PSA <4.0 ng/mL, the second group - PSA >4.0-10.0 ng/mL, the third group- PSA>10.0 ng/mL. The International Prostate Symptom Score *(*IPSS*)* was used to evaluate symptoms, along with the physical examination (including a digital rectal exam or DRE). In the study group with reading of PSA> 4.0 ng/mL prostate biopsy was performed in order to determine the study participants with prostate cancer. Gleason score was used for evaluation of the prostate cancer malignity grade.

25(OH)D in the human serum was determined by the chemiluminescent immunoassay (CLIA) technology using the DiaSorin Liaison XL Analyzer. Vitamin D insufficiency was defined as 25(OH)D level in serum <30 ng/mL, mild vitamin D insufficiency from 20 to 29 ng/mL, pronounced vitamin D insufficiency from 10 to 20 ng/mL, and vitamin D deficiency with 25(OH)D level in serum <10 ng / mL. Vitamin D serum level is considered to be sufficient from 30 to 70 ng/mL, while the potential vitamin D toxicity starts from 25(OH)D serum level > 150 ng / mL.

2.1 Data Acquisition Methods

In order to determine the amount of vitamin D consumed, an interview concerning the quantity and frequency of the consumed food was carried out by means of the “Food Consumption Frequency Questionnaire” used as a research instrument. Quantity of the food consumed by the respondents was determined with the assistance by the photographic atlas of food and food portions (the illustrated methodological material for the nutritional surveys intended for the public, nutritionists, public health and nutrition program students) which was developed by the Ministry of Health of the Republic of Lithuania, at the Republican Food Centre of the Vilnius University, Faculty of Medicine. All the photos were supplied with captures translated into Latvian by the State Agency "Public Health Agency" in 2007.

The Food Consumption Frequency Questionnaire includes 164 types of foodstuffs.

There are:

- 27 items of cereal products;
- 27 items of meat, eggs, fish products;
- 13 items of dairy products;
- 29 items of vegetables and root vegetables;
- 16 items of fruit and berry products;
- The survey included five types of nuts and six kinds of seed;
- 11 types of soups;
- 6 types of dessert;
- 11 types of beverages, including 4 beverage additives;
- 6 types of alcoholic beverages;
- 7 types of dietary fat.

During the interview the respondents were asked how frequently a particular food type was consumed in their daily diet. The Nutritional survey options for the intake of a particular food type were: once a day, several times a day (from 1 to 6 times), 2-4 times a week, 5-6 times a week, 1-3 times a month, once a month or less frequently, never. Special attention was paid to the food products containing vitamin D (fish, dairy products, eggs). The amount of vitamin D in the diet was calculated by the BLS (Bundeslebensmittelschlüssel) Max Rubner Institute German database. The Lifestyle questionnaire was processed by the program developed by the Institute of Food Safety, Animal Health and Environment *”BIOR”.*

The Lifestyle Questionnaire consists of 33 questions. There are 10 general questions, including date of birth, height, weight, education, and marital status of the respondents. There are 13 questions concerning the types of fat used in the diet and the way of fat processing, as well as specific questions highlighting oncological morbidity in the family, known diseases, existing symptoms, use of medications and dietary supplements, sexual activity, and the physical activity frequency table. The questions of sexual and physical activity of the Lifestyle Questionnaire covered not only the current period of life, but also alterations in the activity over the years.

Vitamin D deficiency is widespread throughout the world and is diagnosed in more than 1 billion people. Causes of vitamin D deficiency are well known and often associated with the geographic

region of residence, low insolation, sun power characteristics, malabsorption syndrome, liver and kidney diseases, use of certain medications. Latvia due to the geographical location, ethnic and economic characteristics has all the prerequisites for the high prevalence of deficiency of vitamin D.

Sun exposure is the main source of vitamin D. Vitamin D that is synthesized in the skin is present in serum at least twice longer then vitamin D synthesized via dietary intake. When an adult wearing a bathing suit gets a minimal erythema dose (mild skin redness 24 hours post-sun exposure), a dose of synthesized vitamin D is equal to 10,000 -25,000 IU of vitamin D consumed with the diet. Many factors, including skin pigmentation, age, and sun protection creams can reduce vitamin D synthesis in the skin, as well as latitudes below 33º, especially in winter [10].

Vitamin D deficiency is a common problem worldwide, particularly in the elderly population. The ability to synthesize vitamin D3 is 3-4 times lower in persons over 65 [11].

There are several reasons:

- Cholecalciferol synthesis in the skin after sun exposure becomes less effective with age due to the decrease in 7-dehydrosterol level in the skin;
- Increase in the adipose tissue mass leads to the increased fat-soluble vitamin 25 (OH) D destruction, thus, furthermore, its bioavailability is lowered;

If vitamin D serum level is low, impairment of the 1.25 (OH) 2D (Calcitriol) synthesis occurs due to the lack of substrate, moreover, with age, additionally, the renal function is decreased affecting 25 (OH) conversion to 1.25 (OH) 2D. An active metabolite 1.25 (OH) 2D (Calcitriol) acts through the vitamin D receptor (VDR), with age VDR expression weakens leading to vitamin D resistance in the bones, small intestine and muscular tissue.

All over the world from 40 to 100% of elderly people who do not live in the nursing homes suffer from vitamin D deficiency or insufficiency. Half of the elderly women use vitamin D <137 IU / daily (3.42 mg) that is only ¼ of the recommended daily dose. Approximately 25% of the elderly population take vitamin D supplement <65 IU / day (1.62 g) that is 10.8% of the recommended daily dose [12]. According to the results of the Global Food Consumption Survey that ran from 2007 to 2009 and included the respondents - persons from 17 to 64 years of age, the inhabitants of Latvia on the average take only 1.7 µg or 34% of the recommended vitamin D daily dose (study „Latvian national „food basket", the balance of grocery and agricultural products" 2009).

3. RESULTS

There were 252 men included in the study, the mean age was 59 ±7.9 years old, the mean PSA level 4.3±0.42 ng/mL, BMI 28.4±4.02 kg/m², IPSS 12±0.64, 25(OH)D 17.5±7.46 ng/mL. PSA <4.0 the mean 25(OH)D was 19.95±6.87, PSA 4-10, 25(OH)D 14.31±7.43, PSA >10, 25(OH)D 11.46±3.50.

Table 1. Mean data ± SD for PSA, Age, Weight, 25(OH)D and BMI

PSA (ng/mL)		Age (years)	Weight (kg)	25(OH)D blood serum (ng/mL)	BMI (kg/m²)
<4.0	Mean	59.25	88.85	19.95	28.38
	N	158	158	158	158
	Std. deviation	7.83	13.63	6.87	3.96
4.0-10.0	Mean	59.77	87.95	14.31	28.22
	N	65	65	65	65
	Std. deviatin	8.77	14.48	7.43	4.34
>10.0	Mean	57.06	92.49	11.46	28.81
	N	29	29	29	29
	Std. deviation	5.94	15.24	3.50	3.68
Total	Mean	59.13	89.04	17.52	28.39
	N	252	252	252	252
	Std. deviation	7.91	14.05	7.46	4.02
	P-value	<0.05	<0.001	<0.001	<0.001

PSA- Prostate Specific Antigen, BMI-Body Mass Index
P-value <0.05 is significant, <0.001 highly significant

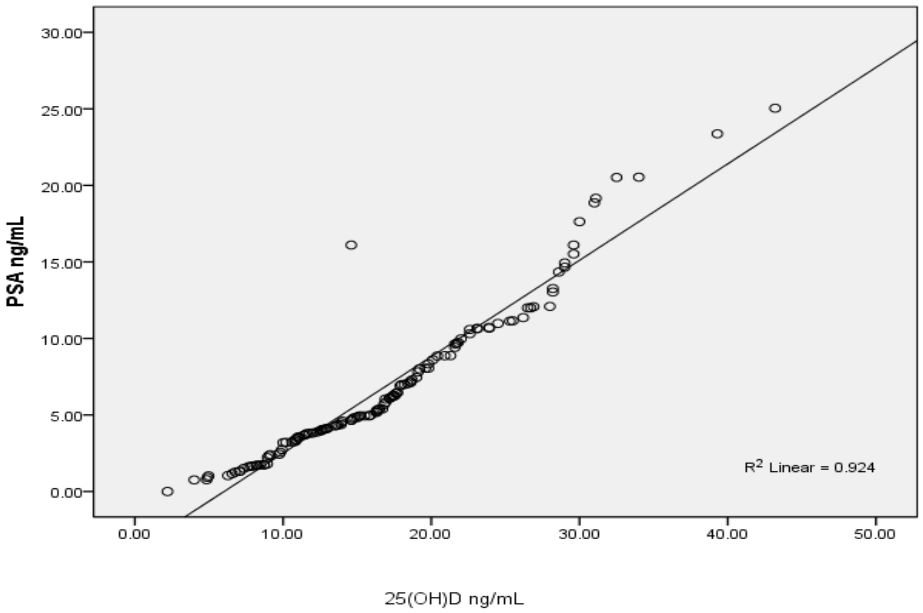

Fig. 1. Correlation between PSA-Prostate Specific Antigen serum level (ng/mL) and vitamin D-25(OH)D serum level (ng/mL)

The Pearson's correlation was statistically insignificant (r = 0.924) (the correlation is significant at p < 0.01 level), correlation between PSA and 25(OH)D in blood serum (ng/mL) was statistically insignificant

There are only a few foods that naturally contain vitamin D. Fatty fish (mackerel, salmon, herring) and cod liver oil are the major sources of vitamin D3 in Latvia (Table 2). Small amounts of vitamin D3 are also present in beef liver, eggs and meat. Some dairy products in Latvia including butter, margarine, and milk are fortified with vitamin D3. Vitamin D2 is found in wild mushrooms and plants.

Table 2. Vitamin D content in both unfortified and fortified foods

Food	µg	IU	% RDD*	% TUL**
Fish meal, 150 g				
Fish liver (cod)	72.4	2900	725	145
Mackerel (salmon, trout, 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 Latvia is 400 IU*

*** Tolerable Upper Limit (TUL) for daily vitamin D intake is 2,000 IU*

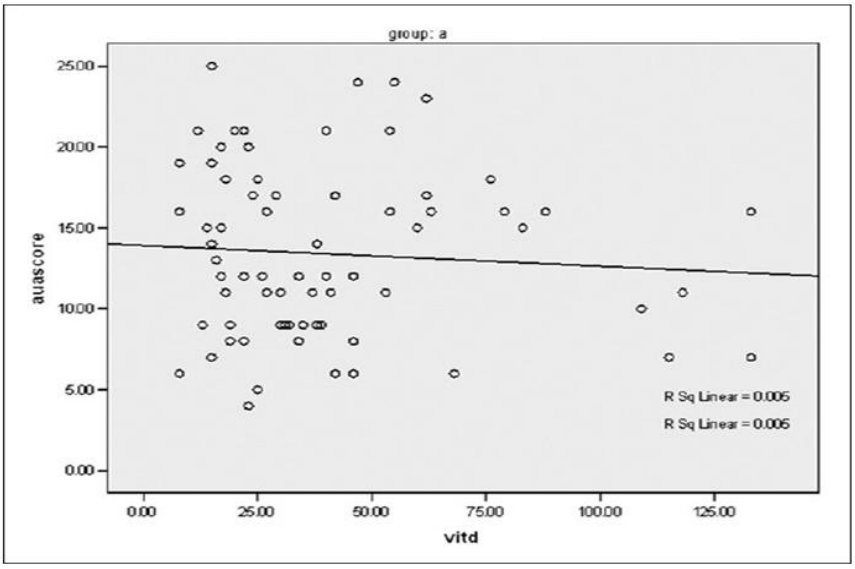

Fig. 2. Correlation between vitamin D and IPSS -International Prostatic Symptoms Score
However, the correlation between IPSS and Vitamin D using Pearson's correlation was statistically insignificant (r = 0.05) (correlation is significant at p< 0.01 level)

4. DISCUSSION

The more research is done on the effects of vitamins and their role in ensuring human health, the more often it is discovered that many diseases are associated with the particular vitamin deficiency. Deficiency in certain nutrients may lead to seasonal depression, apathy and lack of strength, cause immunosuppression and decrease in capacitation, and even to the development of various serious diseases. Vitamin D may also represent such substances.

The results of the study that took place in England showed that vitamin D insufficiency in the population (25 - 70 years old) is present throughout the year and especially pronounced in winter: 73% of participants had vitamin D insufficiency, and 8% were found to have vitamin D deficiency. At summer insufficiency rate in population was as high as 29%, while the deficiency rate was1%. These figures may also apply to the Latvian population [13].

Analyzing the results of the studies that involved persons over 65 years of age, it was found out that 6% of men and 10% of women had 25 (OH) D serum concentrations lower than 25 ng /mL. Vitamin D serum levels were significantly lower in the group with the respondents spending a longer time indoors. Over a third of men and women had 25 (OH) D serum concentrations lower than 25 ng/mL irrespective of seasonal fluctuations [14].

A study conducted England comprised 1.766 participants aged 65 and over, who lived in both private houses and flats. Serum 25 (OH) vitamin D concentrations were lower in males (38.1 ng/mL) and females (36.7 ng/mL), who lived in flats, compared to those males (56.2 ng/mL) and females (48.4 ng/mL), who lived in private houses [15,16,17,18,19].

Some scientists assume that a daily intake of 20000 IU of vitamin D3 can become a significant and safe therapy to limit systemic inflammations and act as cancerous growth inhibitors [20].

GcMAF protein (macrophage-activating factor) is known to support our immune system as a very potential tool to fight cancer. For GcMAF synthesis, a constant supply of the sufficient dose of vitamin D3 is required, and GcMAF protein, in turn, provides inhibition of the development of cancerous cells in the prostate, for example [21,22,23].

UpAR (urokinase receptor) is another substance responsible known to facilitate growth of malignant cells in the prostate, it also contributes to the metastatic process. However, an adequate amount of GcMAF protein inhibits UpAR and thus, the malignancy itself [24,25,26].

Apart from increased consumption in fruits, vegetables and fibers in their daily menu in general, males should limit the consumption of dairy products. Strange and unexpected though it might sound, but that was proved nevertheless by at least 16 studies. The results of two substantial studies conducted at the Harvard University showed: males, who totally excluded the diary products from their diet, were 30% less likely to develop prostate cancer compared to those, who consumed dairy products regularly [27,28].

The explanation is, presumably as follows, consumption of dairy products leads to the increase of insulin-like growth factor (IGF) that is known to actively stimulate growth of cancerous cells [29,30].

The latest studies indicate the link between the increased level of IGF-1 not only in case of prostate cancer, but also in breast cancer [31,32].

Another explanation is linked to the function of vitamin D. Vitamin D that is actually a hormone, helps our body in Calcium absorption from the digestive tract. Besides, it also has protective anti-cancer effect, therefore, helps protect the prostate from cancer.

Vitamin D is synthesized in the skin not only as a result of direct exposure to sunlight, but also through the digestive system, we can get it from certain food products. At this stage it is called pro-vitamin. In order to be activated, it has to be delivered to both the liver and kidneys, where its molecular structure undergoes slight modification.

When Calcium from the diary products gets into the blood stream, organism receives a signal that if the level of Calcium is sufficient, no vitamin D activation is needed for the uptake of the great amount of Calcium, therefore. The level of active vitamin D in blood decreases abruptly. The lower the level of vitamin D is, the greater the risk to develop prostate cancer, consequently. Needless to say, milk can be fortified with vitamin D, however, it is a non-active form called pro-vitamin D, and besides, consumption of dairy products inhibits the activation process of vitamin D in the organism [33].

Finally, consumption of animal fats, no matter dairy or others, leads to the increased testosterone production that is directly linked to the risk of prostate cancer development [34].

One of the studies included 52 males with the non-aggressive form of prostate cancer who underwent a planned prostatectomy. All the excised prostate preparations were examined. Within the 60-day period of observation either vitamin D supplements (4000 IU) or placebo were given randomly. The researchers found out that those males with prostate cancer who received placebo either did not have any changes, or had deterioration of their health conditions [35,36]. To the contrary, those males, who were given vitamin D supplements had improvement in 60% of cases. In some cases a decrease in tumour size was detected, while in others it entirely disappeared.

Moreover, the researchers discovered that the level of several main lipids and proteins was lower in the group of those who received vitamin D supplements. This fact directly proves the decrease of inflammatory activity. The activity of certain proteins, GDF15 (growth differentiation factor 15), for instance, is also known to suppress inflammation. GDF15 serum level was increased significantly by vitamin D [37]. However, as it was reported by the previous studies, very small amount of GDF15 is produced by aggressive prostate tumours. Therefore, such conclusion as vitamin D can at least prevent transformation of non-aggressive cancer form can be drawn.

However, other studies indicated a link between vitamin D intake and decrease in cancer mortality. Even in 2008 the article published by the Proceedings of the National Academy of Sciences it was concluded that duplication of sun exposure time can save10 times more human lives because the sun light is a very powerful means to prevent cancerous diseases [38].

Healthcare specialists recommend sunbathing at least 15 minutes a day for the fair-skinned persons (insolation of the face and bare arms), and 2-3 times longer for those individuals with darker skin in the moderate climates.

5. CONCLUSION

Both vitamin D insufficiency and deficiency and common in males with an increased risk of developing prostate cancer. The increase in PSA levels correlates with the lower vitamin D levels. The correlation between serum 25(OH)D level and overall prostate cancer risk was also found in our study. The life questionnaire and the adapted food frequency questionnaire were

developed and adjusted to the needs of the Latvian nutrition specialists.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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