VILNIUS UNIVERSITY
STATE RESEARCH INSTITUTE CENTRE FOR INNOVATIVE MEDICINE

Vaidilė Strazdienė

ASSOCIATIONS BETWEEN VITAMIN D, BONE MINERAL DENSITY AND PHYSICAL PERFORMANCE IN THE ELDERLY, AND RELATIONSHIP OF *VDR* GENE *Bsm*I POLYMORPHISM WITH SEVERE POSTMENOPAUSAL OSTEOPOROSIS

Summary of doctoral dissertation

Biomedical Sciences, Medicine (06 B)
Gerontology (B 670)

Vilnius, 2013

This dissertation was prepared at the State Research Institute Centre for Innovative Medicine in the period 2008–2012.

Research supervisor:

Prof. Dr. Vidmantas Alekna (Vilnius University, Biomedical Sciences, Medicine – 06B; Gerontology – B670).

Scientific consultant:

Prof. Dr. Marija Tamulaitienė (Vilnius University, Biomedical Sciences, Medicine – 06B; Gerontology – B670).

The dissertation will be defended at the Medical Research Council of Vilnius University:

Chairman:

Prof. Habil. Dr. Jurgis Algirdas Juozulynas (Vilnius University, Biomedical Sciences, Medicine – 06B; Gerontology – B670).

Members:

Prof. Dr. Dainius Characiejus (Vilnius University, Biomedical Sciences, Medicine – 06B; Cytology, Oncology, Cancerology – B200);

Prof. Dr. Janina Didžiapetrienė (Vilnius University, Biomedical Sciences, Medicine – 06B; Cytology, Oncology, Cancerology – B200);

Prof. Dr. Jūratė Macijauskienė (Lithuanian University of Health Sciences, Biomedical Sciences, Medicine – 06B; Gerontology – B670);

Assoc. Prof. Dr. Birutė Žilaitienė (Lithuanian University of Health Sciences, Biomedical Sciences, Medicine – 06B; Gerontology – B670).

Opponents:

Prof. Habil. Dr. Vita Lesauskaitė (Lithuanian University of Health Sciences, Biomedical Sciences, Medicine – 06B; Gerontology – B670);

Dr. Diana Mieliauskaitė (State Research Institute Centre For Innovative Medicine, Biomedical Sciences, Medicine – 06B; Gerontology – B670);

The dissertation will be defended at the open session of the Medical Research Council on June 10, 2013 at 12:00 in the Conference Hall of State Research Institute Centre for Innovative Medicine. Address: Zygimantu str. 9, Vilnius, Lithuania.

The summary of the doctoral dissertation was sent on May ___, 2013.

The dissertation in full text is available at the libraries of Vilnius University and State Research Institute Centre for Innovative Medicine.

VILNIAUS UNIVERSITETAS
VALSTYBINIS MOKSLINIŲ TYRIMŲ INSTITUTAS INOVATYVIOS MEDICINOS CENTRAS

Vaidilė Strazdienė

SENYVO AMŽIAUS ŽMONIŲ VITAMINO D, KAULŲ MINERALŲ TANKIO IR FIZINIO PAJĖGUMO SĄSAJOS BEI *VDR* GENO *Bsm*I POLIMORFIZMO RYŠYS SU SUNKIA POMENOPAUZINE OSTEOPOROZE

Daktaro disertacijos santrauka

Biomedicinos mokslai, medicina (06 B)
Gerontologija (B 670)

Vilnius, 2013

Disertacija rengta 2008–2012 metais Valstybiniame mokslinių tyrimų institute Inovatyvios medicinos centre.

Mokslinis vadovas:
prof. dr. Vidmantas Alekna (Vilniaus universitetas, biomedicinos mokslai, medicina – 06B, gerontologija – B670).

Konsultantė:
prof. dr. Marija Tamulaitienė (Vilniaus universitetas, biomedicinos mokslai, medicina – 06B, gerontologija – B670).

Disertacija ginama Vilniaus universiteto Medicinos mokslo krypties taryboje:

Pirmininkas:
prof. habil. dr. Jurgis Algirdas Juozulynas (Vilniaus universitetas, biomedicinos mokslai, medicina – 06B; gerontologija – B670).

Nariai:
prof. dr. Dainius Characiejus (Vilniaus universitetas, biomedicinos mokslai, medicina –06B; citologija, onkologija, kancerologija – B200);

prof. dr. Janina Didžiapetrienė (Vilniaus universitetas, biomedicinos mokslai, medicina – 06B; citologija, onkologija, kancerologija – B200);

prof. dr. Jūratė Macijauskienė (Lietuvos sveikatos mokslų universitetas, biomedicinos mokslai, medicina – 06B; gerontologija – B670);

doc. dr. Birutė Žilaitienė (Lietuvos sveikatos mokslų universitetas, biomedicinos mokslai, medicina – 06B; gerontologija – B670).

Oponentai:
prof. habil. dr. Vita Lesauskaitė (Lietuvos sveikatos mokslų universitetas, biomedicinos mokslai, medicina – 06B; gerontologija – B670);

dr. Diana Mieliauskaitė (Valstybinis mokslinių tyrimų institutas Inovatyvios medicinos centras, biomedicinos mokslai, medicina – 06B; gerontologija – B670).

Disertacija bus ginama viešame Medicinos mokslo krypties tarybos posėdyje 2013 m. birželio 10 d. 12 val. Valstybinio mokslinių tyrimų instituto Inovatyvios medicinos centro konferencijų salėje. Adresas: Žygimantų g. 9, Vilnius, Lietuva.

Disertacijos santrauka išsiuntinėta 2013 m. gegužės ___ d.

Disertaciją galima peržiūrėti Vilniaus universiteto ir Valstybinio mokslinių tyrimų instituto Inovatyvios medicinos centro bibliotekose.

ABBREVIATIONS

25(OH)D	–	25-hydroxyvitamin D
BMD	–	bone mineral density
BMI	–	body mass index
CI	–	confidence interval
DNA	–	deoxyribonucleic acid
PCR	–	polymerase chain reaction
PTH	–	parathyroid hormone
r	–	correlation coefficient
SD	–	standard deviation
SPPB	–	short physical performance battery
VDR	–	vitamin D receptor

1. INTRODUCTION

Vitamin D is of great scientific interest over the last decade due to a wide variety of its functions in the human body. Although vitamin D is known as a "vitamin", some scientists name it a steroid hormone due to its secosteroid structure and its impact on the muscles, balance and neuromuscular function, inflammation, immune processes, and gene activity. The vitamin D receptors are found in the most human tissue cells. Skeletal muscle cells also contain the vitamin D receptors, they are found both in cell membrane and in nucleus. Vitamin D deficiency is associated with many diseases and pathological conditions, e.g. cardiovascular diseases, diabetes, and cancer.

Vitamin D deficiency is a widespread problem throughout the world. In elderly the prevalence of vitamin D deficiency may be up to 90%. The elderly are at the risk for vitamin D deficiency for several reasons: tendency to avoid the sun, decreased skin capacity to produce vitamin D, and diminished intestinal absorbtion.

Until recently, studies investigating vitamin D have focused on its impact on bone health and calcium homeostasis. Vitamin D influences the fracture risk in two ways: by reducing the risk of falls and increasing the bone mineral density. Even asymptomatic vitamin D deficiency is now considered as one of the most important factors that influences integrity of bone tissue, as it causes secondary hyperparathyroidism which increases rate of bone remodelling. The relationship of vitamin D and bone mineral density is influenced by numerous contributing factors, including geographic location, racial and ethnic differences, sun exposure, and dietary vitamin D consumption. Some authors do not found the association between vitamin D and bone mineral density.

Evidence for vitamin D deficiency contribution to physical performance and muscle mass is also conflicting. Some researchers have found that vitamin D deficiency is significantly associated with muscle weakness, loss of muscle mass, reduced physical performance, balance problems and gait abnormalities, increased risk of falls and fractures in elderly, but other do not point out to such results. Vitamin D influences muscle function by regulating cellular calcium transport, use of inorganic phosphate for formation of active phosphate derivatives, and protein synthesis in muscle.

In the past decade performed scientific researches provided contradictory conclusions about vitamin D and falls relationship.

The main risk factors of osteoporosis and its clinical manifestations – low-trauma fractures – include age, hormonal, environmental, lifestyle characteristics, and genetic factors may increase the influence of environmental and hormonal factors. It was found that microstructure and biochemical parameters of bone tissue, level of calcium in the bones, peak bone mass, bone mineral density, and age-related bone loss are determined by genetic factors. Twin and family studies suggest that 50–85% of the variance in bone mineral density and microstructure and 40–60% of the variance in biochemical markers of bone turnover could be genetically determined. It was found that osteoporotic fracture risk doubles in individuals with parental hip fracture history. Over 100 candidate genes associated with bone mineral density and the risk of osteoporosis have already been identified. Vitamin D receptor (*VDR*) gene is a nuclear transcription factor that mediates the action of 1,25$(OH)_2$D3 (the active metabolite of vitamin D), thus affecting calcium absorption, bone remodeling and mineralization rate. The sequence of *VDR* gene was revealed to be polymorphic for different individuals. Since the pioneering work of N.A. Morrison in 1994 demonstrating the association of the *VDR* gene *Bsm*I polymorphism with bone mineral density, numerous subsequent papers have been published on that topic. Their results have been inconclusive; still there is no clear answer whether specific *VDR* genotype is associated with lower bone mineral density and higher fracture risk.

1.1. The aim of the research

The aim of this study was to analyze associations between vitamin D, bone mineral density and physical performance in the elderly, and to evaluate the relationship of *VDR* gene *Bsm*I polymorphism with severe postmenopausal osteoporosis.

1.2. The objectives of the research

1. To evaluate vitamin D, bone mineral density, muscle mass, and physical performance features in elderly according to age and gender.

2. To analyze the associations between vitamin D, bone mineral density, physical performance, muscle mass and falls.
3. To investigate the relationship of *VDR* gene *Bsm*I polymorphism with severe postmenopausal osteoporosis.

1.3. Scientific novelty

In this scientific research still contraversial associations between vitamin D, bone mineral density, falls, muscle mass and physical performance have been analysed. The links we have found between vitamin D and bone mineral density contribute to numerous scientific studies supporting this connection. Also, in our study we observed the positive association between vitamin D and physical performance. We believe that it is appropriate to investigate vitamin D levels in the blood in the elderly persons, especially those over the age of 80, and in person with low bone mineral density, as well as in those experienced falls. We have found that low muscle mass and strength, low gait speed significantly associated with falls in elderly.

Results of this research revealed association between *VDR* gene *Bsm*I polymorphism and bone mineral density in women with severe postmenopausal osteoporosis. Currently, the studies of human populations' gene pools in different geographical regions are relevant and are already carried out in many countries. It is believed that the human genotype studies in the future will be used for assessment of individual risk of bone fractures and in selection the optimal treatment for osteoporosis.

2. SUBJECTS AND METHODS

2.1. Study population

The sample size was calculated by SAS Power and Sample Size 12.1 statistical program. Persons who have applied to the National Osteoporosis Center were invited to participate in the study. Inclusion criteria were: the age of 60 years and older, voluntary consent to participate in the study. Exclusion criteria were: an objection to any procedure, large dose of radiation received over the past 12 months, conditions and diseases known to affect muscle metabolism and muscle strength, malignant tumours of various localizations, mental disorders, current/past using of any medications likely to affect muscle and bone metabolism or taking any vitamin D supplements. Written informed consent was obtained from each participant. The study was approved by the Regional Biomedical Research Ethics Committee (Approval No. 158200-04-291-76, issued on 6 April 2011).

2.2. Methods

Each subject was interviewed by the investigator. The demographic and social data, lifestyle factors were recorded in the questionnaire, as well as the medical history about past/current diseases, using of any medications was taken from each subject. The subjects were asked about falls – whether or not they had fallen during the past year, and, if so how many times. Falls were defined as "landing on the floor or ground without violent causes from standing height".

Antropometry. The height and body weight were measured barefoot and in light indoor clothes with a stadiometer and an electronical medical scale to the nearest 0.1 cm and 0.05 kg, respectively. Body mass index (BMI) was calculated as weight in kilograms divided by the height in meters squared (kg/m^2).

Measurement of vitamin D and parathyroid hormone. Blood sampling was performed after fasting for at least 12 hours. Serum 25-hydroxyvitamin D (25(OH)D) and parathyroid hormone (PTH) were measured by automated immunoassay (Cobas E411, Roche Diagnostic). After the blood had clotted at room temperature but not more than 1 hour after the collection of serum samples for 15 min. were centrifuged at room temperature and 1500 rev./min. with Labofuge centrifuge. Immediately after the separation of serum, the samples were stored at -20˚ C till examination, but no more than a week. After thawing, samples were immediately examined for the vitamin D and PTH. Analysis was carried out by fully automated electrochemical luminescence immunoassay method using the original reagents, and in accordance with the manufacturer's instructions, regular calibration and quality control applied on a daily basis.

Subjects were divided into two groups by vitamin D level, according to the recommendations of the Institute of Medicine of National Academies: vitamin D deficiency group (vitamin D levels in blood less than 20 ng/ml), an individuals with serum concentration ≥of 20 ng/ml were considered as vitamin D sufficient. Also the cohort was divided into four vitamin D level in blood groups using quartiles.

Assessment of physical performance. A short physical performance battery (SPPB) based on the lower-extremity performance tests, was used to assess physical performance. The SPPB consisted of walking speed, ability to stand up a chair, and ability to maintain balance in progressively more challenging positions. Walking speed was defined in time (seconds) of 4 m walk at usual pace. Participants were allowed to use canes. For the standing balance test, participants were asked to stand in three progressively more difficult positions for 10 seconds each: a side-by-side position, a semi-tandem position, and a full-tandem position. To test the ability to stand up a chair, participants were asked to stand up and sit down a chair as quickly as possible in five times with their hands folded across their chest; time (in seconds) to complete the test was recorded.

Muscle strength measurement. Handgrip strength was measured using a handheld dynamometer („Presision", Druck, Germany). Participants were asked to perform the task three times with the dominant hand. The average of all results obtained was used for the analysis.

Bone mineral density, muscle mass measurement. Bone mineral content, bone mineral density, lean mass, regional muscle mass were measured by dual-energy x-ray absorptiometry (iDXA, GE Lunar, USA). Appendicular skeletal muscle mass calculation was based on the sum of muscle mass in all four limbs. Bone mineral density (BMD) was measured in the total body, lumbar spine (L_1–L_4, in the anterior-posterior direction), and in the left hip. BMD was expressed in absolute numbers (g/cm^2), as well as by the T-score.

Genotyping. For genetic analyses venous blood sample was taken from cubital vein using Vacutainer system (Beckton-Dickinson, Franklin Lakes, NJ, USA). Deoxyribonucleic acid (DNA) was isolated from bloodspots dried on special *NucleoSafe* cards (Macherey-Nagel, Germany) using standard proteinase K digestion, phenol-chloroform extraction and ethanol precipitation. The DNA solution was extracted with a phenol chloroform isoamyl alcohol mixture to remove protein contaminants, and then precipitated with 100% ethanol. The DNA was pelleted after the precipitation step, washed with 70% ethanol to remove salts and small organic molecules, and resuspended in buffer at a concentration suitable for further investigation. *Bsm*I, polymorphism of *VDR* gene was determined using polymerase chain reaction (PCR) analysis using specially designed primers.

2.3. Statistical methods

Statistical analysis was performed using Windows software package SPSS 18.0. Mean of variables, standard deviation (SD) were calculated. To assess normality of distribution of interval variables Kolmogorov-Smirnov test was applied. Mean differences of interval variables were compared using Student t–test. The one-way analysis of variance (ANOVA) was used to determine whether there were any significant differences between the means of three or more independent groups and the difference between these groups was established by Bonferroni test. Spearman correlation coefficient was used to calculate relations between the interval variables. For the assessment of effect of independent factors to the evaluation of dependent variable and prediction of the values of the dependent variable stepwise multivariate linear regression and logistic regression analysis was used. For the assesment of falls relation with other variables cluster analysis was used. The differences were considered statistically significant if α error probability (p value) was less than 0.05.

3. RESULTS

3.1 Vitamin D, bone mineral density, muscle mass, and physical performance features in elderly according to age and gender

A total of 392 individuals, 151 (38.5%) men (from 60 to 95 years) and 241 (61.5%) women (from 60 to 89 years) were included in this study. We compared anthropometric parameters, vitamin D, parathyroid hormone, bone mass, bone mineral density, muscle mass and physical performance in the elderly men and women. The results are presented in Table 1.

Table 1. Anthropometric, vitamin D, parathyroid hormone, bone mass, bone mineral density, muscle mass and physical performance characteristics according to gender

Parameters	Men (n = 151)		Women (n = 241)		p
	Mean±SD	95% CI for mean	Mean±SD	95% CI for mean	
Age, years	72.86±8.01	71.58-74.15	72.67±7.52	71.71-73.62	0.803
Height, cm	172.53±6.81	171.43-173.62	158.13±6.66	157.28-158.97	<0.001
Body mass, kg	81.69±13.92	79.45-83.93	70.72±13.38	69.02-72.42	<0.001
BMI, kg/m²	27.40±4.12	26.73-28.06	28.33±5.28	27.65-29	0.067
Vitamin D, ng/ml	16.74±10.14	15.11-18.37	16.34±8.14	15.22-17.47	0.685
PTH, μg/ml	52.69±25.55	48.58-56.79	54.59±30.46	50.62-58.55	0.527
Lean mass, kg	54.0±6.65	52.93-55.08	40.22±5.23	39.53-40.91	<0.001
Appendicular muscle mass, kg	24.39±3.69	23.79-24.98	18.14±3.2	17.69-18.58	<0.001
Leg muscle mass, kg	17.63±2.69	17.19-18.06	13.43±2.23	13.14-13.73	<0.001
Arm muscle mass, kg	6.76±1.13	6.57-6.94	4.54±1.12	4.39-4.69	<0.001
Bone mineral content, kg	2.99±0.47	2.92-3.07	2.04±0.38	1.99-2.09	<0.001
Total body BMD, g/ cm²	1.185±0.172	1.157-1.213	1.005±0.183	0.979-1.03	<0.001
Lumbar BMD, g/cm²	1.215±0.229	1.179-1.252	1.016±0.191	0.991-1.04	<0.001
Total hip BMD, g/cm²	1.015±0.163	0.988-1.041	0.868±0.183	0.845-0.891	<0.001
Femur neck BMD, g/cm²	0.926±0.154	0.901-0.95	0.825±0.141	0.807-0.843	<0.001
Handgrip strength, kg	31.22±10.63	29.49-32.95	14.58±6.59	13.66-15.51	<0.001
Balance test, s	9.58±1.12	9.39-9.76	9.58±1.34	9.39-9.77	0.98
Walking test, s	4.99±2.22	4.62-5.35	6.86±7.09	5.86-7.85	0.002
Five repeated chair stand test, s	15.08±5.56	14.17-15.99	19.56±8.44	18.37-20.75	<0.001

p-value was calculated using Student t test.
SD – standard deviation; CI – confidence interval; BMI – body mass index; PTH – parathyroid hormone; BMD – bone mineral density.

It was found that age did not differ statistically significantly between men and women, but men's height and body weight were higher than women's. We haven't found significant differences of serum vitamin D and PTH values between men and women. It was found that lean mass, arm and leg muscle mass was significantly higher of men, comparing with women. Bone density parameters, measured in all areas, were higher in the group of men, comparing with women. Handgrip strength, gait speed, time of five repeated chair stand test was also significantly higher in men. We have not found significant differences in balance between men and women.

When performing analysis of differences in vitamin D and parathyroid hormone levels in the different age groups we recorded the following trends: with age increase, vitamin D levels in blood have decreased, and parathyroid hormone levels have increased (Fig. 1).

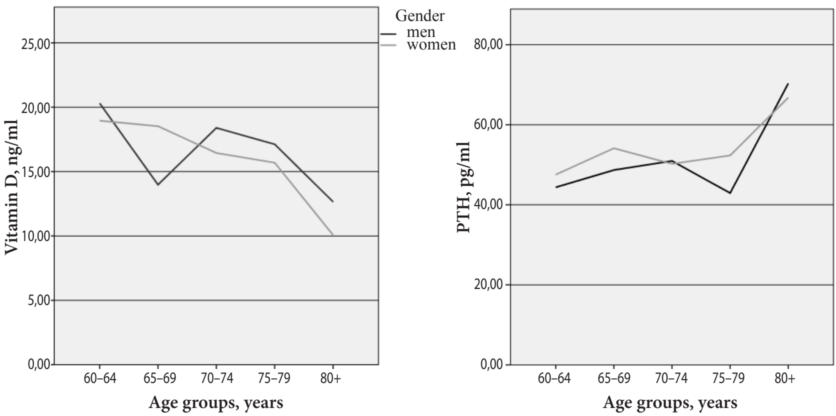

Figure 1. Vitamin D and parathyroid hormone levels in different groups of age in elderly persons

It was found that vitamin D levels differed significantly between the age groups of both men ($p=0.002$) and women ($p<0.001$) groups. Parathyroid hormone levels also differed significantly between the different age groups (men, $p<0.001$, women $p=0.014$). The vitamin D levels of women aged 80 years and older were the lowest (10.07±4.88 ng/ml), and significantly differed from the 75–79 year old women (15.69±4.78 ng/ml, $p=0.001$), 70–74 year old women (16.44±7.48 ng/ml, p<0.001), 65–69 year old women (18.53±6.32 ng/ml, p<0.001), and 60–64 year old women (18.96±7.54 ng/ml, p<0.001).

It was observed that vitamin D levels of men aged 80 years and older (12.65±8.63 ng/ml) significantly differed from men aged 70–74 years (18.4±8.43 ng/ml, p=0.006), and 60–64 year old men (20.31±8.87 ng/ml, p<0.001).

We compared bone mineral mass and density and parameters between two vitamin D level groups, separately for men and women. The results are presented in Table 2.

Table 2. Bone mineral mass and density according to gender and vitamin D level

Parameters	Men			Women		
	Vit. D level <20ng/ml **(n=99)**	Vit. D level ≥20ng/ml **(n=52)**	**p**	Vit. D level < 20 ng/ml **(n=174)**	Vit. D level ≥20ng/ml **(n=67)**	**p**
Bone mineral content, kg	2.92±0.45	3.13±0.48	0.01	2.06±0.4	2.12±0.3	0.17
Total body BMD, g/ cm^2	1.161±0.13	1.229±0.22	0.05	0.989±0.201	1.043±0.133	0.03
Lumbar BMD, g/cm^2	1.183±0.223	1.277±0.24	0.02	1.039±0.191	1.053±0.165	0.61
Total hip BMD, g/cm^2	0.994±0.164	1.055±0.16	0.03	0.88±0.221	0.924±0.124	0.05
Femur neck BMD, g/cm^2	0.908±0.151	0.958±0.16	0.06	0.834±0.151	0.862±0.11	0.16

Results are expressed as mean±standard deviation; p-value was calculated using Mann-Whitney test.
BMD – bone mineral density.

It was found that bone mineral content (2.92±0.45 kg), total body BMD (1.161±0.13 g/cm^2), lumbar BMD (1.183±0.223 g/cm^2), and total hip BMD (0.994±0.164 g/cm^3) was significantly lower in men with vitamin D deficiency, comparing with men whose vitamin D levels were ≥20 ng/ml. There was no significantly difference in femoral neck BMD between vitamin D level groups. It was observed that total body BMD (0.989±0.201 g/cm^2) and total hip BMD (0.88±0.221 g/cm^2) was significantly lower of women with vitamin D deficiency, comparing with women whose vitamin D levels were ≥20 ng/ml. There was no significantly difference in bone mineral content, lumbar BMD and femoral neck BMD between vitamin D level groups.

We compared muscle mass and performance parameters between two vitamin D level groups, separately for men and women. The results are presented in Table 3.

Table 3. Skeletal muscle mass and physical performance according to gender and vitamin D level

Parameters	Men			Women		
	Vit. D level <20ng/ml **(n=99)**	Vit. D level ≥20ng/ml **(n=52)**	**p**	Vit. D level < 20 ng/ml **(n=174)**	Vit. D level ≥20ng/ml **(n=67)**	**p**
Age, years	74.09±7.96	70.25±7.32	0.004	73.49±7.67	69.08±7.67	<0.001
BMI, kg/m^2	27.37±4.38	27.54±3.6	0.8	28.61±5.29	28.48±5.29	0.87
Vitamin D, ng/ml	11.11±4.21	27.55±9.3	<0.001	12.52±4.56	26.38±4.56	<0.001
PTH, pg/ml	54.94±21.78	44.81±15.79	0.004	56.98±33.69	46.54±33.6	0.03
Lean mass, kg	53.56±6.77	54.86±6.45	0.26	40.63±5.5	39.92±4.7	0.39
Appendicular muscle mass, kg	23.99±3.64	25.18±3.73	0.06	18.24±3.42	17.87±3.42	0.46
Arm muscle mass, kg	6.67±1.15	6.92±1.11	0.21	4.62±1.29	4.5±1.29	0.53
Leg muscle mass, kg	17.32±2.6	18.26±2.78	0.04	13.62±2.35	13.37±2.35	0.47
Handgrip strength, kg	30.62±10.63	32.66±10.58	0.27	14.11±6.98	15.79±6.98	0.11
Balance test, s	9.5±1.2	9.70±0.88	0.19	9.43±1.49	9.96±1.49	0.01
Walking test, s	5.1±1.9	4.95±2.78	0.89	7.28±8.22	5.75±8.22	0.17
Five repeated chair stand test, s	15.17±6.16	14.82±4.2	0.72	19.92±9.52	18.66±9.52	0.35

Results are expressed as mean±standard deviation; p-value was calculated using Mann-Whitney test.
BMI – body mass index; PTH – parathyroid hormone.

Our findings indicate that handgrip strength, lean mass, appendicular muscle mass, and arm muscle mass did not differ statistically significantly among men of different vitamin D groups. We found that leg muscle mass was lower in vitamin D deficiency group (<20 ng/ml) men (17.32±2.6, p=0.04), comparing with men whose vitamin D levels were higher or equal to 20 ng/ml. Muscle strength and muscle mass parameters did not differ statistically significantly between women of two vitamin D groups. We also found that for women in vitamin D deficiency group the balance test time was shorter (9.43±1.49 s), compared with women, whose vitamin D levels were higher than 20 ng/ml (p=0.01).

For a closer analysis of the differences in bone mineral density, muscle mass and strength, physical performance with regard to vitamin D levels, we divided the cohort into four vitamin D level in blood groups using quartiles (the results are presented in Tables 4 and 5).

Table 4. Bone mineral mass and density according to gender and vitamin D level quartiles

Parameters	Vitamin D level quartiles				p
	1	2	3	4	
Men					
Sample	**n=39**	**n=37**	**n=38**	**n=37**	-
Bone mineral content, kg	2.77±0.51	3.1±0.41	2.99±0.45	3.13±0.46	0.004
Total body BMD, g/ cm²	1.107±0.145	1.202±0.118	1.223±0.13	1.210±0.246	0.013
Lumbar BMD, g/cm²	1.167±0.255	1.23±0.21	1.196±0.206	1.275±0.239	0.204
Total hip BMD, g/cm²	0.93±0.177	1.049±0.146	1.039±0.153	1.046±0.151	0.002
Femur neck BMD, g/cm²	0.847±0.159	0.968±0.142	0.942±0.147	0.948±0.146	0.003
Women					
Sample	**n=61**	**n=60**	**n=59**	**n=61**	-
Bone mineral content, kg	1.97±0.39	2.10±0.4	2.08±0.39	2.15±0.3	0.101
Total body BMD, g/ cm²	0.939±0.238	1.032±0.134	1.000±0.189	1.049±0.133	0.013
Lumbar BMD, g/cm²	1.042±0.23	1.062±0.188	1.014±0.155	1.055±0.161	0.587
Total hip BMD, g/cm²	0.862±0.141	0.914±0.155	0.861±0.273	0.932±0.125	0.118
Femur neck BMD, g/cm²	0.81±0.141	0.859±0.173	0.829±0.128	0.871±0.112	0.11

Data are presented as mean±standard deviation; p-values were calculated by using ANOVA test.
BMD – bone mineral density.

Analysis of variance (ANOVA) showed that bone mineral content, total body BMD, total hip, femoral neck bone mineral density were significantly different in groups of men obtained using quartiles of vitamin D levels, however BMD in the lumbar spine area did not differ. Post hoc analysis using the Bonferroni criterion showed that men's bone mineral content in the first quartile of vitamin D level was the lowest (2.77±0.51 kg) and significantly differed from bone mineral mass in the second (p=0.013) and fourth quartile men (p=0.006). Total hip BMD was the lowest in the first vitamin D quartile men (0.93±0.177 g/cm²) and significantly differed from the second (p=0.008), third (p=0.018) and fourth (p=0.01) quartiles men. Femoral neck BMD was lowest in first vitamin D quartile men (0.847±0.159 g/cm²) and differed significantly from the second (p=0.004), third (p=0.042), and fourth (p=0.025) quartiles men.

Table 5. Skeletal muscle mass and physical performance according to gender and vitamin D level quartiles

Parameters	Vitamin D level quartiles				p
	1	2	3	4	
Men					
Sample	**n=39**	**n=37**	**n=38**	**n=37**	-
Vitamin D, ng/ml	6.57±1.24	12.27±1.27	18.32±2.26	30.32±9.75	<0.001
PTH, pg/ml	60.84±22.7	53.84±22.04	46.77±17.61	44.15±14.75	0.001
Lean mass, kg	51.24±6.73	55.95±6.09	54.23±6.59	54.62±6.61	0.018
Appendicular muscle mass, kg	22.68±3.58	25.16±3.3	24.67±3.74	25.1±3.76	0.01
Arm muscle mass, kg	6.25±1.1	7.07±1.04	6.84±1.18	6.86±1.09	0.013
Leg muscle mass, kg	16.43±2.58	18.09±2.39	17.84±2.68	18.23±2.82	0.014
Handgrip strength, kg	28.±11.53	32.22±9.38	32.89±10.18	32.28±10.95	0.166
Balance test, s	9.49±1.04	9.64±1.09	9.43±1.49	9.79±0.77	0.559
Walking test, s	5.16±1.84	4.79±1.84	5.38±3.45	4.57±0.93	0.419
Five repeated chair stand test, s	15.77±6.16	15.1±5.68	14.27±6.37	15.04±3.58	0.718
Women					
Sample	**n=61**	**n=60**	**n=59**	**n=61**	-
Vitamin D, ng/ml	7.32±1.85	13±1.37	18.2±1.64	27.07±6.92	<0.001
PTH, pg/ml	58.66±25.14	55.03±23.94	49.16±26.61	47.98±16.18	0.074
Lean mass, kg	40.17±5.61	41.03±5.12	40.19±5.9	40.31±4.67	0.829
Appendicular muscle mass, kg	17.96±3.81	18.23±3.08	18.27±3.32	18.07±2.53	0.96
Arm muscle mass, kg	4.62±1.51	4.46±.83	4.68±1.4	4.58±0.69	0.796
Leg muscle mass, kg	13.34±2.5	13.77±2.35	13.59±2.19	13.49±1.97	0.81
Handgrip strength, kg	12.69±6.44	13.66±8.06	16.03±5.57	15.95±5.45	0.023
Balance test, s	9.45±0.92	9.19±2.03	9.74±1.14	9.95±9.75	0.024
Walking test, s	7.37±4.68	8.29±12.74	5.93±2.34	5.78±2.24	0.234
Five repeated chair stand test, s	21.18±11.78	20.07±9.05	18.62±6.61	18.4±4.6	0.324

Data are presented as mean±standard deviation; p-values were calculated by using ANOVA test. PTH – parathyroid hormone.

Our study revealed that lean mass, appendicular muscle mass, leg muscle mass, arm muscle mass statistically significantly differed between men in vitamin D level quartiles. Hand muscle strength, balance, 4-meter walking test, sit-and-stand from a chair test statistically did not significantly differ between vitamin D quartiles in men. Post hoc analysis showed that lean mass was the lowest in the first quartile of vitamin D level in men (51.24±6.73 kg) and it was significantly different for the second (p=0.013) quartile. Appendicular muscle mass was the lowest in the first quartile of vitamin D in men (22.68±3.58 kg) and differed from the second (p=0.021) and fourth (p=0.029) quartiles. Chair test results do not differ significantly between vitamin D quartiles. Arm muscle mass was the lowest in the first quartile of vitamin D level in men (6.25±1.1 kg) and was significantly different for the second (p=0.011) quartile. Leg muscle mass was the lowest in the first quartile of vitamin D in men (16.43±2.58 kg) and was significantly different from the second (p=0.043), and fourth (p=0.023) men's quartiles.

Women lean mass, appendicular muscle mass, leg muscle mass, and arm muscle mass did not differ statistically significantly in vitamin D level groups. We observed differences of handgrip strength and balance test in vitamin D quartiles in women. Balance test time in the fourth quartile (9.95±9.75 s) was significantly longer than in the second quartile (9.19±2.03 s, p=0.015).

Total body bone mineral density differences in the vitamin D level quartiles for men and women are provided in Figure 2.

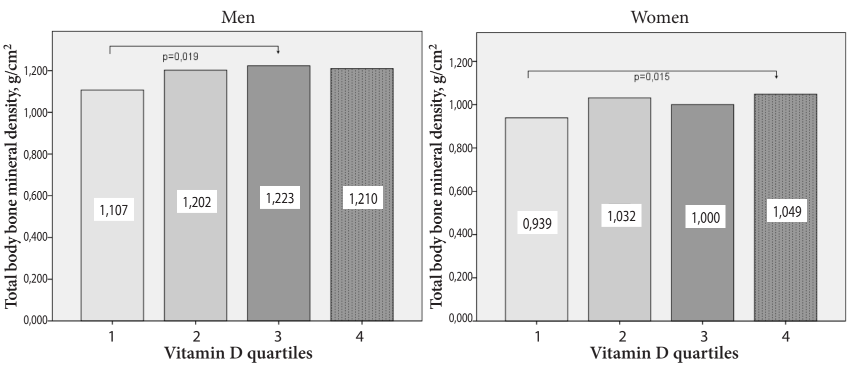

Figure 2. Total body mineral density according to vitamin D quartiles and gender

Total body BMD was significantly different in vitamin D quartiles both for studied men and women. When applying a post hoc Bonferroni criterion for univariate analysis of variance (ANOVA), we have found that total body BMD in the first quartile of vitamin D level in men (1.107±0.145 g/cm^2)

was significantly lower compared to the third vitamin D men's quartile (p=0.019). Total body BMD (0.939±0.238 g/cm^2) was significantly lower in first vitamin D quartile women, comparing with the fourth vitamin D quartile women (1.049±0.133 g/cm^2, p=0.015).

Summarising these results we can conclude, that vitamin D deficiency has been found in most of the investigated elderly people: 72.2% of women and 65.6% of men. The lowest vitamin D level was observed in persons aged 80 years and older. We observed significant bone mass, bone mineral density, muscle mass and physical performance differences in vitamin D levels groups.

3.2. The associations between vitamin D, bone mineral density, muscle mass, physical performance and falls in elderly

In order to analyse associations between vitamin D, bone mineral density, muscle mass and physical performance, correlation analysis was performed (Table 6).

Table 6. Correlations between vitamin D, bone mineral density, skeletal muscle mass, strength and physical performance

Parameters	Vitamin D			
	Men		Women	
	r	p	r	p
PTH	-0.29	0.001	-0.24	0.001
Bone mineral content	0.25	0.002	0.13	0.06
Total body BMD	0.34	0.001	0.16	0.03
Lumbar BMD	0.16	0.04	0.11	0.94
Total hip BMD	0.28	0.001	0.14	0.04
Femur neck BMD	0.26	0.002	0.14	0.04
Lean mass	0.16	0.04	0.08	0.91
Appendicular muscle mass	0.22	0.007	0.04	0.57
Arm muscle mass	0.17	0.03	0.05	0.5
Leg muscle mass	0.25	0.002	0.03	0.67
Handgrip strength	0.15	0.07	0.24	0.001
Balance test	0.16	0.06	0.25	<0.001
Walking test	-0.1	0.21	-0.15	0.03
Five repeated chair stand test	-0.78	0.35	-0.13	0.06

r – Spearman correlation coefficient.

BMD – bone mineral density; PTH – parathyroid hormone.

The results of this analysis showed that vitamin D level was statistically significantly negatively associated with parathyroid hormone of men and women. Significant correlations between vitamin D and bone mineral density were detected in men; however there were no significant relationships between vitamin D and lumbar BMD in women. A weak positive correlations of vitamin D with total BMD (r=0.16, p=0.03), femoral neck BMD (r=0.14, p=0.04) and hip BMD (r=0.14, p=0.04) were observed in women. Significant positive associations between vitamin D and muscle mass in the all measured regions (appendicular muscle mass, lean mass, arm muscle strength, leg muscle mass) were found in men. These relations were not significant in women.

Handgrip strength did not correlate statistically significantly with vitamin D in men. When analysing the women's data, we observed a significant correlation between handgrip strength and vitamin D. Vitamin D levels significantly negatively correlated with parathyroid hormone (p=0.001). It was found positive relationship of vitamin D and bone mineral density in men; the strongest correlation was found between vitamin D levels and total body BMD. A significant positive correlation between vitamin D and total body BMD was also observed in women (Figure 3).

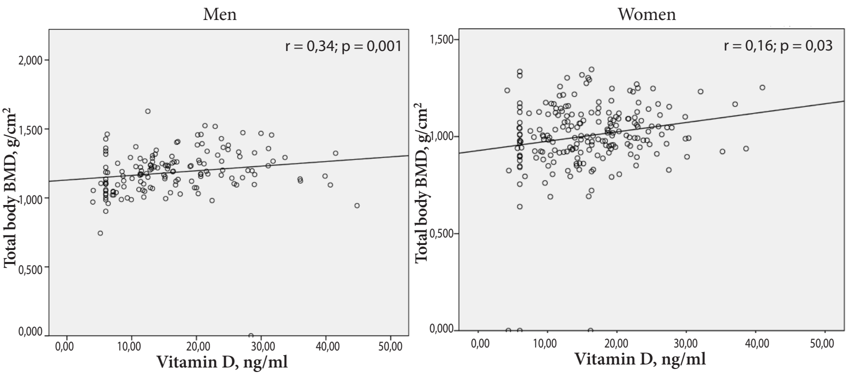

Figure 3. Correlations between vitamin D level and total body BMD of men and women

We also analysed relation between falls and vitamin D levels, muscle mass and physical performance for elderly men and women. We determined that 22 (14.8%) men fell once, twice a year fell one man (0.7%), three or more times – four (2.6%) men, and 122 (81.9%) men never fell during the past year. Once per year fell 54 (27.4%) women, 7 women (3.6%) fell twice a year, while 11 (5.5%) women fell three or more times; 125 (63.5%) women have not fell during the past year.

There was no statistically significant difference between the age of fallers and non-fallers. Associations between vitamin D, muscle mass, physical performance and falls are described in Table 7.

Table 7. Bone mineral density, vitamin D, skeletal muscle mass, strength and physical performance in fallers and non – fallers

Parameters	Fallers (n=99)	Non-fallers (n=247)	p
Bone mineral content, kg	2.32±0.53	2.53±0.64	0.004
Total body BMD, g/cm^2	1.085±0.204	1.133±0.229	0.072
Lumbar BMD, g/cm^2	0.873±0.149	0.883±.154	0.576
Total hip BMD, g/cm^2	0.929±0.14	0.954±0.202	0.256
Femur neck BMD, g/cm^2	1.061±0.189	1.096±.191	0.125
Vitamin D, ng/ml	16.01±7.81	16.07±8.04	0.945
PTH, pg/ml	59.13±38.36	51.43±23.24	0.023
Age, years	72.85±7.31	72.43±8.02	0.652
Lean mass, kg	43.64±7.8	47.35±9.21	0.001
Appendicular muscle mass, kg	20.02±4.35	21.16±4.68	0.04
Arm muscle mass, kg	5.26±1.67	5.63±1.53	0.05
Leg muscle mass, kg	14.77±2.89	15.53±3.26	0.045
Handgrip strength, kg	17.96±10.74	23.23±12.01	<0.001
Balance test, s	9.60±1.18	9.57±1.28	0.832
Walking test, s	7.40±9.5	5.52±2.7	0.005
Five repeated chair stand test, s	18.4±7.76	17.36±7.65	0.257

Data are presented as mean ± standard deviation; p- value was calculated using Student t test.
BMD – bone mineral density; PTH – parathyroid hormone.

We have found that bone mineral mass, lean mass, arms, legs, and appendicular muscle mass were significantly lower of people who experienced falls, comparing to non-fallers. Vitamin D levels did not differ statistically significantly between the groups, but parathyroid hormone levels (51.43±23.24 pg/ml) was statistically significantly higher of fallers comparing with group in patients that did not experience falls during the past year (59.13±38.36 pg/ml, p=0.023). It was found that handgrip strength (23.23±12.01 kg) was significantly higher of non-fallers, comparing with persons, who experienced falls (17.96±10.74 kg, p<0.001). For the people who experienced falls, it was also reported a significantly longer the 4-meter walking test performance time (7.40±9.5 s) compared to the people who did not fall during the past year (5.52±2.70 s, p=0.005).

In order to distinguish the groups of the studied patients we employed two-step cluster analysis. With its aid the subjects were divided into the 7 following clusters (results are presented in Table 8).

Table 8. Falls cluster analysis

Parameters	Clusters						
	1	2	3	4	5	6	7
Sample (%)	40 (11.7)	59 (17.3)	54 (15.8)	54 (15.8)	64 (18.7)	35 (10.2)	36 (10.5)
Falls	+	-	-	-	-	-	-
Gender	women	women	women	women	men	men	men
Appendicular muscle mass, kg	18.27	17.09	17.88	20.21	23.48	27.56	23.94
Total hip BMD, g/cm^2	0.842	0.873	0.935	0.935	0.994	1.097	1.031
Vitamin D, ng/ml	12.2	12.82	26.39	11.61	10.88	17.72	28.65
PTH, ng/ml	73.02	50.55	46.81	57.49	52.78	49.82	45.19

Quantitative characteristics are presented as mean.
BMD – bone mineral density; PTH– parathyroid hormone.

After analysing the research results, two groups (the first and the seventh) of patients were distinguished. Into the first group (n = 40) fell the most (95%) number of people. Most of them (70%) were women, which were characterized as having lower appendicular muscle mass (18.27 kg), lower hip BMD (0.842 g/cm^2), lower vitamin D levels (12.2 ng/ml), and the highest parathyroid hormone levels in blood (73.02 ng/ml) in formed groups. The majority of the seventh group were men who did not experience fall during the past year (80% did not experience falls), whose vitamin D levels were the highest (28.65 ng/ml), and parathyroid hormone levels were the lowest (45.19 ng/ml). Hip BMD (1.031 g/cm^2), and appendicular muscle mass was highest of these men, compared with other groups.

Our study results showed, that vitamin D was significantly positively associated with handgrip strength of women and with muscle mass of men, as well with BMD in elderly people of both gender. Muscle mass, handgrip strength and gait speed were associated with falls of elderly people. Cluster analysis showed that the group of the most frequent fallers consisted of women, whose vitamin D levels in the blood were low (12.2 ng/ml), they also featured low muscle mass and low total hip bone mineral density (0.842 g/cm^2). The non–faller group consisted mainly of men, whose vitamin D levels in blood were close to optimal (28.65 ng/ml), they also had high muscle mass and hip bone mineral density (1.031 g/cm^2).

3.3. The relationship of *VDR* gene *Bsm*I polymorphism with severe postmenopausal osteoporosis

In this study two groups of participants – women with severe osteoporosis and control women group was analyzed.

Table 9. Studied parameters differences in severe osteoporosis women and control women group

Parameters	Severe osteoporosis women group (n=56)	Control group (n=83)	p
Age, years	74.12±6.43	72.9±5.95	0.424
Body mass, kg	64.28±11.75	75.15±10.48	<0.001
Height, cm	155.49±6.23	159.0±5.5	0.003
Vitamin D, ng/ml	12.62±5.34	16.02±7.39	0.026
PTH, pg/ml	57.44±24.81	47.32±16.27	0.08
Lumbar BMD, g/cm^2	0.878±0.146	1.095±0.119	<0.001
Total hip BMD, g/cm^2	0.741±0.101	0.869±0.085	<0.001
Femur neck BMD, g/cm^2	0.745±0.097	0.949±0.099	<0.001

Data are presented as mean±standard deviation; p- value was calculated using Student t test.
BMD – bone mineral density; PTH – parathyroid hormone.

There was no statistically significant difference of age between women with severe osteoporosis and control group women. Lumbar, total hip and femoral neck BMD were significantly lower in severe osteoporotic women compared to controls.

The frequency of *VDR Bsm*I genotypes in women with severe osteoporosis and group of control women are shown in table 10.

Table 10. The frequency of *VDR Bsm*I genotypes in women with severe osteoporosis and group of control women

***VDR Bsm*I genotype**	**Severe osteoporosis women group (n = 28)**	**Control group (n = 45)**	**χ2**	**p**	**OR (95 % CI)**
bb	9 (32.1%)	22 (48.9%)			1.29 (0.87-1.91)
Bb	14 (50%)	17 (37.8%)	10.95	0.371	1.01 (0.53-1.88)
BB	5 (17.9%)	6 (13.3%)			1.31 (0.72-2.33)

VDR – vitamin D receptor gene; OR – odds ratio; CI – confidence interval.

It was found that 9 (32.1%) women with severe osteoporosis and 22 (48.9%) control women have *VDR Bsm*I *bb* genotype. *VDR Bsm*I *Bb* genotype was evaluated in 14 (50%) women with severe osteoporosis and 17 (37.8%) control group women. The data revealed that only 5 (17.9%) women with severe osteoporosis and 6 (13.3%) control group women have *VDR Bsm*I *BB* genotype. There was no statistically significant difference of *VDR Bsm*I genotypes between women with severe osteoporosis and controls.

It was found that total hip and femoral neck BMD are not significantly different between *Bsm*I genotypes of women with severe osteoporosis and controls. However, lumbar BMD is significantly higher in the *BB* genotype to compare with the *bb* genotype and *Bb* genotype of women with severe osteoporosis (Figure 4).

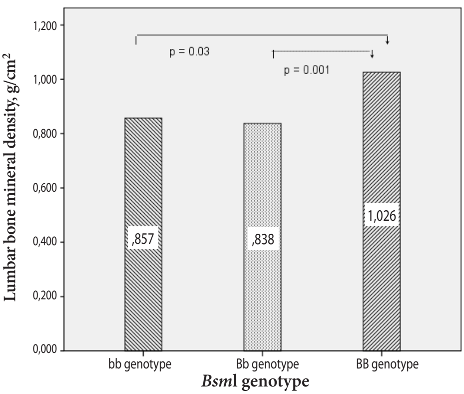

Figure 4. Lumbar BMD depending on *VDR Bsm*I genotypes in women with severe osteoporosis

It was found that lumbar BMD is not significantly different between *VDR Bsm*I genotypes in control women. A Spearman's correlation coefficient was calculated to evaluate the correlation between vitamin D, PTH and BMD depending on *VDR Bsm*I genotypes in women with severe osteoporosis and control women. Data are presented in table 11.

Table 11. Correlation between vitamin D, parathyroid hormone and bone mineral density depending on *VDR Bsm*I genotypes

Parameters	Severe osteoporosis women group (n = 28)				Control group (n = 45)			
	Vitamin D		PTH		Vitamin D		PTH	
	r	p	r	p	r	p	r	p
	bb **(n=9)**				***bb*** **(n=22)**			
Vitamin D	-	-	-0.76	0.02	-	-	0.02	0.92
Lumbar BMD, g/cm^2	-0.23	0.55	0.18	0.64	0.22	0.36	0.11	0.62
Total hip BMD, g/cm^2	0.55	0.13	-0.58	0.1	0.09	0.72	0.02	0.94
Femur neck BMD, g/cm^2	0.66	0.05	-0.33	0.38	0.22	0.36	-0.1	0.65
	Bb **(n=14)**				***Bb*** **(n=17)**			
Vitamin D	-	-	0.4	0.6	-	-	-0.18	0.51
Lumbar BMD, g/cm^2	0.63	0.37	-0.73	0.83	0.57	0.20	0.3	0.25
Total hip BMD, g/cm^2	0.4	0.6	0.11	0.75	0.01	0.98	0.23	0.37
Femur neck BMD, g/cm^2	0.2	0.8	0.19	0.58	0.24	0.36	0.04	0.88

r – Spearman correlation coefficient;
BMD – bone mineral density; PTH – parathyroid hormone.

The table shows that women in severe osteoporosis *VDR Bsm*I *bb* genotype group vitamin D concentration moderately negatively related to PTH, also vitamin D is moderately positively related to femoral neck BMD. There were no statistically significant correlations between vitamin D and lumbar BMD or total hip BMD parameters in *bb* or *Bb* genotypes in either women with severe osteoporosis or control women.

In concluding we can state, that total hip and femoral neck BMD are not significantly different between *Bsm*I genotypes of women with severe osteoporosis and controls. In women with severe postmenopausal osteoporosis, the bone mineral density of lumbar spine was significantly higher in the *VDR Bsm*I gene *BB* genotype bearers comparing to the *bb* and *Bb* genotype bearers. The moderate positive correlation was found between the femoral neck BMD and vitamin D in women with severe postmenopausal osteoporosis bearing *VDR Bsm*I gene *BB* genotype.

4. CONCLUSIONS

1. Vitamin D deficiency has been found in most of the investigated elderly people: 72.2% of women and 65.6% of men. The lowest vitamin D level was observed in persons aged 80 years and older. It was found that bone mineral density of men and women, muscle mass in men and physical performance in women were significantly lower in those with vitamin D level less than 20 ng/ml, comparing with vitamin D sufficiency group.
2. Vitamin D statistically significantly positively associated with handgrip strength of women and with muscle mass of men, as well with BMD in elderly people of both gender. Muscle mass, handgrip strength and gait speed were associated with falls of elderly people. Cluster analysis showed that the most frequent fallers group consisted of women, whose vitamin D levels in the blood were low (12.2 ng/ml), they also featured low muscle mass and low total hip bone mineral density (0.842 g/cm^2). The non–faller group consisted mainly of men, whose vitamin D levels in blood were close to optimal (28.65 ng/ml), they also had high muscle mass and hip bone mineral density (1.031 g/cm^2).
3. In women with severe postmenopausal osteoporosis, the bone mineral density of lumbar spine was significantly higher in the *VDR Bsm*I gene *BB* genotype bearers comparing to the *bb* and *Bb* genotype bearers. The moderate positive correlation was found between the femoral neck BMD and vitamin D in women with severe postmenopausal osteoporosis bearing *VDR Bsm*I gene *BB* genotype.

SUMMARY IN LITHUANIAN

Įvadas

Pastarąjį dešimtmetį vitaminas D kelia didelį mokslininkų susidomėjimą dėl įvairių jo funkcijų žmogaus organizme. Nors vitaminas D vadinamas „vitaminu“, dėl jo sekosteroidinės struktūros ir poveikio į raumenis, neuroraumeninę funkciją ir pusiausvyrą, imuninius procesus, uždegimą ir genominį poveikį kurie mokslininkai jį vadina steroidiniu hormonu. Žmogaus organizme vitamino D receptoriai yra randami daugelio audinių ląstelėse. Skeleto raumenų ląstelėse taip pat yra nustatyta esant vitamino D receptorių, jie randami ir ląstelės membranoje, ir branduolyje. Vitamino D trūkumas siejamas su daugeliu ligų ir patologinių būklių – širdies ir kraujagyslių ligomis, cukriniu diabetu, onkologiniais susirgimais. Vitamino D trūkumas kraujyje nustatomas daugelio šalių gyventojams ir yra ypatingai paplitęs nuo pusiaujo nutolusiose teritorijose. Net iki 90 proc. senyvo amžiaus asmenų vitamino D koncentracija kraujyje nepakankama. Senstant vitamino D ima trūkti dėl per trumpo buvimo saulėje, sumenkusio odos sugebėjimo gaminti vitaminą D ir prastesnio jo pasisavinimo iš žarnyno.

Iki šiol atliktuose moksliniuose darbuose, analizuojančiuose vitamino D funkcijas žmogaus organizme, daugiausiai buvo ištirtas vitamino D ryšys su kaulų “sveikata” ir kalcio homeostaze. Vitaminas D kaulų lūžių riziką veikia dvejopai: sumažindamas griuvimų riziką ir didindamas kaulų mineralų tankį. Net ir besimptominis vitamino D trūkumas šiuo metu laikomas vienu iš svarbiausių kaulinio audinio vientisumą lemiančių veiksnių, kadangi sukelia antrinę hiperparatirozę, kuri didina kaulinio audinio remodeliacijos greitį. Tačiau vitamino D koncentracijos kraujyje ir kaulų mineralų tankio ryšio stiprumą įtakoja ir daugybė kitų veiksnių: geografinė padėtis, rasiniai ir etniniai skirtumai, saulės ekspozicija, su maistu gaunamo vitamino D kiekis. Kai kuriems tyrėjams sąsajų tarp vitamino D koncentracijos kraujyje ir kaulų mineralų tankio nepavyko nustatyti.

Mokslinių tyrimų, kuriuose buvo analizuotos vitamino D ir fizinio pajėgumo bei raumenų masės sąsajos, rezultatai taip pat nevienareikšmiai. Dalis tyrėjų teigia, kad senyvo amžiaus asmenims vitamino D trūkumas yra reikšmingai susijęs su raumenų silpnumu, raumenų masės sumažėjimu, sumažėjusiu fiziniu aktyvumu, pusiausvyros ir eisenos sutrikimais, didinančiais griuvimų ir lūžių riziką, tačiau kiti mokslininkai tokių rezultatų nenurodo. Vitaminas D veikia raumenų funkciją reguliuodamas kalcio transportą ląstelėje, neorganinio fosfato panaudojimą aktyvių fosfatinių darinių susidarymui, ir baltymų sintezę raumenyse. Yra atlikta mokslinių tyrimų, kuriais nustatytos tiesioginės vitamino D sąsajos su raumenų mase, tačiau įrodyta, kad anabolinis poveikis yra tik esant vitamino D trūkumui. Pastaraisiais dešimtmečiais mokslininkai, atliekantys mokslinius tyrimus, kuriose buvo vertinamos vitamino D ir griuvimų sąsajos, pateikdavo prieštaringas išvadas.

Osteoporozės ir jos klinikinės išraiškos – mažos traumos sukeltų kaulų lūžių – pagrindiniai rizikos veiksniai yra amžius, hormoniniai, aplinkos ir gyvenimo būdo ypatumai, tačiau genetiniai veiksniai gali padidinti aplinkos veiksnių ir hormonų įtaką. Nustatyta, kad genetiniai veiksniai lemia kaulinio audinio mikrostruktūrą ir biocheminius parametrus, kalcio kiekį kauluose, kaulų masės piko susidarymą, kaulų mineralų tankį ir su amžiumi susijusį kaulų masės netekimą. Šlaunikaulio lūžis, įvykęs tėvams, padvigubina osteoporozinio lūžio tikimybę palikuonims. Tiriant dvynius ir šeimas įrodyta, kad genetiniai veiksniai įtakoja kaulų dydį, šlaunikaulio geometrinius parametrus, apie 50–85 proc. kaulų mineralų tankio bei kaulų mikroarchitektūros pokyčių, 40–60 proc. kaulinio audinio apykaitos biocheminių žymenų koncentracijos pokyčių. Nustatyta daugiau nei 100 kandidatinių genų, susijusių su kaulų mineralų tankiu ir osteoporozės rizika.

Vitamino D receptoriaus (*VDR*) genas yra branduolio transkripcijos faktorius, kuris reguliuoja $1{,}25(OH)_2D3$, aktyviosios vitamino D formos, veikimą, ir įtakoja kalcio absorbciją, kaulų remodeliacijos ir mineralizacijos procesus. Buvo atskleista, kad skirtingų asmenų *VDR* geno deoksiribonukleorūgšties sekos varijuoja, yra polimorfiškos. N. A. Morison su bendraautoriais 1994 metais pirmasis atliko tyrimą, kuriame buvo nustatytos vitamino D receptoriaus geno *Bsm*I polimorfizmo ir kaulų mineralų tankio sąsajos. Vėliau atliktų mokslinių tyrimų išvados apie osteoporozės genetinius veiksnius yra nevienareikšmės; vis dar nėra aišku, ar kuris nors konkretus *VDR* genotipas yra susijęs su mažesniu kaulų mineralų tankiu ir didesne lūžių rizika.

Darbo tikslas

Išanalizuoti senyvo amžiaus žmonių vitamino D koncentracijos kraujyje sąsajas su kaulų mineralų tankiu ir fiziniu pajėgumu bei įvertinti *VDR* geno *Bsm*I polimorfizmo ryšį su sunkia pomenopauzine osteoporoze.

Darbo uždaviniai

1. Nustatyti senyvo amžiaus žmonių vitamino D koncentracijos kraujyje, kaulų mineralų tankio, raumenų masės ir fizinio pajėgumo ypatumus atsižvelgiant į amžių ir lytį.
2. Išanalizuoti senyvo amžiaus žmonių vitamino D koncentracijos kraujyje, kaulų mineralų tankio, fizinio pajėgumo, raumenų masės ir griuvimų tarpusavio sąsajas.
3. Įvertinti vitamino D receptoriaus geno *Bsm*I polimorfizmo ryšį su sunkia pomenopauzine osteoporoze.

Mokslinis darbo naujumas ir aktualumas

Atliekant šį mokslinį tyrimą buvo vertinamos iki šiol pilnai neištirtos vitamino D koncentracijos sąsajos su kaulų mineralų tankiu, griuvimais, taip pat analizuojamos sąsajos su raumenų masės ir fizinio pajėgumo rodikliais. Atlikus šį tyrimą nustatytos vitamino D receptoriaus geno *Bsm*I polimorfizmo sąsajos su kaulų mineralų tankiu esant sunkiai pomenopauzinei osteoporozei. Šiuo metu atskirų geografinių regionų populiacijų genofondo tyrimai yra aktualūs ir jau atliekami daugelyje šalių. Mūsų žiniomis, Lietuvoje iki šiol nebuvo atlikta osteoporozės genetinių tyrimų, todėl šio tyrimo rezultatai papildys Europos šalyse atliekamų tyrimų, kuriuose tiriami atskirų regionų ir etninių grupių genetinius osteoporozės veiksnius, rezultatus. Manoma, kad žmogaus genotipo tyrimai ateityje bus naudojami vertinant individualią kaulų lūžių riziką ir parenkant optimalų osteoporozės gydymą.

Mūsų nustatytos sąsajos tarp vitamino D koncentracijos ir kaulų mineralų tankio prisideda prie daugybės mokslinių darbų, patvirtinančių šį ryšį. Taip pat nustatėme teigiamą vitamino D koncentracijos koreliaciją su fiziniu pajėgumu. Todėl manome, kad vitamino D koncentraciją kraujyje tikslinga tirti senyvo amžiaus asmenims, ypač vyresniems nei 80-ies metų, taip pat patyrusiems griuvimus žmonėms bei tiems, kurių mažas kaulų mineralų tankis.

Tirti asmenys ir tyrimo metodai

Imties tūris skaičiuotas naudojant statistinių programų paketą SAS Power and Sample Size 12.1. Tyrime dalyvauti buvo pasiūlyta asmenims, kurie kreipėsi į Nacionalinį osteoporozės centrą. Įtraukimo į tyrimą kriterijai: 60 metų ir vyresnis amžius; savanoriškas sutikimas dalyvauti tyrime. Neįtraukimo į tyrimą kriterijai: Nesutikimas atlikti kurios nors tyrimo procedūros; per pastaruosius 12 mėnesių gauta didelė jonizuojančiosios apšvitos dozė; atramos-judėjimo sistemos ir nervų ligos, sutrikdančios judėjimo funkcijas; bet kurios lokalizacijos vėžiniai susirgimai; psichikos ligos; vaistų, veikiančių raumeninio, riebalinio ir kaulinio audinių apykaitą, vartojimas; vitamino D papildų vartojimas.

Vilniaus regioninis biomedicininių tyrimų etikos komitetas 2011-04-06 išdavė leidimą atlikti biomedicininį tyrimą, leidimo Nr. 158200-04-291-76.

Tiriamųjų apklausa buvo vykdoma tiesiogiai, tyrėjui apklausos rezultatus fiksuojant anketoje. Joje buvo registruojami demografiniai duomenys, socialiniai ir gyvensenos veiksniai, medicininė anamnezė. Taip pat buvo klausiama, ar tiriamasis per praėjusius kalendorinius metus buvo griuvęs, jei griuvo – kiek kartų.

Tiriamųjų ūgis, kūno masė buvo matuojami tiriamiesiems nusirengus viršutinius rūbus, nusiavus batus. Apskaičiuotas kūno masės indeksas (KMI), kūno masę kilogramais padalijus iš ūgio metrais, pakelto kvadratu.

Rankų raumenų jėga matuota dominuojančioje rankoje, naudojant mechaninį dinamometrą. Analizei buvo naudotas trijų matavimų rezultatų vidurkis. Fizinis pajėgumas buvo vertinamas atliekant trumpajį fizinio pajėgumo testų rinkinį (angl. *short physical performance battery*; santrumpa SPPB). Šį testų rinkinį sudaro eisenos greičio, gebėjimo atsistoti nuo kėdės, gebėjimo išlaikyti pusiauvyrą vis daugiau jėgų reikalaujančiose padėtyse įvertinimai.

Kaulų mineralų tankis (KMT), kaulų mineralų masė, raumenų masė tirta dvisrautės radioabsorbciometrijos (angl. *dual-energy x-ray absorptiometry*; *DXA*) metodu *GE Lunar* firmos (JAV) kaulų mineralų tankio matuokliu *iDXA*. KMT buvo išreikštas absoliučiais skaičiais (g/cm^2), vertintas T-lygmuo, kurio apskaičiavimui naudoti gamintojo pateikti referentiniai KMT duomenys. Išmatavus kūno sudėtines dalis, galūnių raumenų masė apskaičiuota pagal formulę: abiejų rankų liesoji masė (kg) + abiejų kojų liesoji masė (kg).

Tiriamiesiems kraujo mėginys buvo imamas ryte, prieš tai nevalgius dvylika valandų. Vitamino D (25OH)D) ir parathormono koncentracija serume tirta pilnai automatizuotu elektrocheminės liuminescencinės imuninės analizės metodu, *Roche Diagnostic* imunologiniu analizatoriumi Cobas E411.

Genetiniams tyrimams kraujo mėginiai buvo imami iš alkūninės venos. Per 5 min. po kraujo paėmimo kraujo ėminys (apie 2 ml) buvo užlašinamas ant specialių *NucleoSafe* kortelių (Macherey-Nagel, Germany). Genetiniai tyrimai buvo atlikti Baltarusijos nacionalinės mokslų akademijos Genetikos ir citologijos instituto molekulinės genetikos laboratorijoje. Tiriamų asmenų deoksiribonukleininė r. (DNR) buvo išskirta iš periferinio kraujo, išdžiovinto ant specialių kortelių standartiniu proteinazės K skaidymo, fenolio–chloroformo–etanolio alkoholio precipitacijos metodu.

Statistinė duomenų analizė atlikta naudojant *SPSS 18.0 for Windows* programų paketą. Pateikiant aprašomąją statistiką intervaliniams kintamiesiems buvo skaičiuoti vidurkiai ir standartiniai nuokrypiai, kokybiniams – dažniai. Dviejų grupių intervalinių kintamųjų vidurkių skirtumai buvo palyginti naudojant Stjudento t kriterijų. Trijų grupių vidurkiai ir jų dispersijos lygintos naudojant vienfaktorinę dispersinę analizę (ANOVA). Esant reikšmingiems skirtumams tarp grupių buvo atliekami poriniai *post hoc* palyginimai, naudojant *Bonferroni* kriterijų. Tiesiniams ryšiams tarp intervalinių kintamųjų nustatyti skaičiuoti Spearman‘o koreliacijos koeficientai (r). Siekiant įvertinti nepriklausomų kintamųjų poveikį priklausomiems kintamiesiems, sudarinėti įvairūs daugialypės tiesinės ir logistinės regresijos modeliai. Tiriant griuvimų ryšį su kitais rodikliais, naudotas dvipakopės klasterinės analizės metodas. Skirtumai laikyti statistiškai reikšmingais, jeigu palyginimui naudoto kriterijaus p reikšmė buvo mažesnė už 0,05 ($p<0{,}05$). Visur pateikiamos dvipusės p reikšmės.

Rezultatai

Ištirti 392 asmenys, iš jų – 151 (38,5 proc.) vyras (nuo 60 iki 95 metų amžiaus) ir 241 (61,5 proc.) moteris (nuo 60 iki 89 metų amžiaus). Nustatyta, kad vyrų ir moterų amžius statistiškai reikšmingai nesiskyrė, tačiau vyrų ūgis ir kūno masė buvo didesni negu moterų. Kūno masės indeksas tarp lyčių reikšmingai nesiskyrė. Vitamino D ir parathormono koncentracija kraujyje vyrams ir moterims taip pat reikšmingai nesiskyrė. Vyrų viso kūno liesoji masė, rankų bei kojų raumenų masės buvo statistiškai reikšmingai didesnės nei moterų; kaulų tankio rodikliai, matuoti visose srityse buvo reikšmingai didesni vyrų grupėje. Rankų raumenų jėga, eisenos greitis, atsisėdimų – atsistojimų nuo kėdės testo laikas taip pat buvo reikšmingai didesni vyrams, nei moterims, tačiau reikšmingo skirtumo tarp lyčių, lygindami pusiausvyrą, nenustatėme.

Analizuojant vitamino D ir parathormono koncentracijos skirtumus amžiaus grupėse stebėjome tokias tendencijas: didėjant amžiui vitamino D koncentracija kraujyje mažėjo, o parathormono – didėjo. Taikydami dispersinės analizės post hoc Bonferroni kriterijų nustatėme, kad 80 metų ir vyresnio amžiaus moterų vitamino D koncentracija buvo mažiausia (10,07±4,88 ng/ml) lyginant su kitomis amžiaus grupių moterimis, ir reikšmingai skyrėsi nuo 75–79 metų moterų (15,69±4,78 ng/ml; p=0,001), 70–74 metų amžiaus moterų (16,44±7,48 ng/ml; p<0,001), 65–69 metų amžiaus moterų (18,53±6,32 ng/ml; p<0,001) ir 60–64 metų moterų (18,96±7,54 ng/ml; p<0,001). Vitamino D koncentracija 80 metų ir vyresnio amžiaus vyrams (12,65±8,63 ng/ml) reikšmingai skyrėsi nuo 70–74 metų amžiaus vyrų (18,4±8,43 ng/ml; p=0,006) ir 60–64 metų vyrų (20,31±8,87 ng/ml; p<0,001), nors reikšmingo skirtumo nuo 65–69 metų amžiaus (13,98±7,37 ng/ml; p=0,519) ir 75–79 metų vyrų (17,12±9,21; p=0,065) nestebėjome.

Analizavome kaulų mineralų masės, kaulų mineralų tankio rodiklių ypatumus atsižvelgiant į vitamino D koncentraciją kraujyje. Vyrams, kurių vitamino D koncentracija buvo mažesnė nei 20 ng/ml, buvo nustatyta statistiškai reikšmingai mažesnė kaulų mineralų masė (2,92±0,45 kg), viso kūno KMT (1,161±0,13 g/cm^2), KMT stuburo slankstelių srityje (1,183±0,223 g/cm^2), bendro šlaunikaulio KMT (0,994±0,164 g/cm^3) lyginant su vyrais, kurių vitamino D koncentracija didesnė arba lygi 20 ng/ml. Šlaunikaulio kaklo KMT statistiškai reikšmingai tarp tiriamųjų vitamino D koncentracijos grupių nesiskyrė.

Moterims, kurių vitamino D koncentracija buvo mažesnė nei 20 ng/ml, buvo nustatytas statistiškai reikšmingai mažesnis viso kūno KMT (0,989±0,201 g/cm^2), bendras šlaunikaulio KMT (0,88±0,221 g/cm^2), lyginant su moterimis, kurių vitamino D koncentracija didesnė arba lygi 20 ng/ml. Statistiškai reikšmingo skirtumo tarp vitamino D koncentracijos grupių nebuvo lyginant kaulų mineralų masės, stuburo KMT ir šlaunikaulio kaklo KMT rodiklius. Mūsų tyrimo rezultatai rodo, kad vyrų rankų raumenų jėga, liesoji masė, galūnių raumenų masė, rankų raumenų masė statistiškai reikšmingai tarp tirtų vitamino D koncentracijos kraujyje grupių nesiskiria. Analizuojant duomenis, nustatėme, kad vyrų vitamino D trūkumo (<20 ng/ml) kojų raumenų masė yra mažesnė (17,32±2,6 kg, p=0,04), lyginant su vyrais, vyrais, kurių vitamino D koncentracija didesnė arba lygi 20 ng/ml.

Moterų raumenų jėgos ir masės rodikliai vitamino D grupėse statististiškai reikšmingai nesiskyrė. Nustatėme, kad moterims vitamino D trūkumo grupėje pusiausvyros testo laikas buvo trumpesnis (9,43±1,49 s), lyginant su moterimis, kurių vitamino D koncentracija kraujyje buvo didesnė nei 20 ng/ml (p=0,01).

Norėdami išanalizuoti sąsajas tarp vitamino D koncentracijos, kaulų mineralų tankio, raumenų masės ir fizinio pajėgumo, atlikome koreliacinę analizę. Šios analizės rezultatai parodė, kad vitamino D koncentracija kraujyje statistiškai reikšmingai neigiamai siejosi su parathormono koncentracija kraujyje tiek vyrams, tiek moterims. Vyrams nustatytos reikšmingos sąsajos tarp vitamino D ir visų kaulų tankio rodiklių. Moterims nustatyta silpna teigiama vitamino D koncentracijos kraujyje koreliacija su viso kūno KMT (r=0,16, p=0,03), su šlaunikaulio kaklo KMT (r=0,14, p=0,04) ir šlaunikaulio viršutinės dalies KMT (r=0,14, p=0,04). Vyrams buvo nustatytos reikšmingos sąsajos tarp vitaminos D ir raumenų masės rodiklių visose matuotose srityse: galūnių raumenų masė, liesoji masė, rankų raumenų jėga, kojų raumenų masė teigiamai, silpnai koreliuoja su vitamino D koncentracija kraujyje. Moterims šios sąsajos buvo nereikšmingos – galūnių raumenų masė, liesoji masė, rankų raumenų jėga, kojų raumenų masė su vitamino D koncentracija kraujyje reikšmingai nekoreliavo. Rankų raumenų jėga vyrams su vitamino D koncentracija statistiškai reikšmingai nesisiejo. Analizuojant moterų duomenis, stebėjome reikšmingas sąsajas tarp rankų raumenų jėgos ir vitamino D koncentracijos kraujyje. Vitamino D koncentracija reikšmingai neigiamai siejosi su parathormono koncentracija kraujyje (p=0,001). Vyrams nustatytos statistiškai reikšmingos koreliacijos visose analizuotose kaulų mineralų tankio srityse, stipriausia koreliacija buvo nustatyta tarp vitamino D ir viso kūno KMT. Moterims taip pat stebėta reikšminga teigiama koreliacija tarp vitamino D ir viso kūno KMT.

Analizavome tyrime dalyvavusių senyvo amžiaus vyrų ir moterų griuvimų sąsajas su vitamino D koncentracija kraujyje, raumenų masės ir fizinio pajėgumo parametrais. Siekdami išskirti charakteringas tirtų pacientų grupes, pasitelkėme dviejų pakopų klasterinę analizę. Jos pagalba tiriamieji buvo suskirstyti į 7 klasterius. Iš visų tirtų grupių išsiskyrė dvi (pirmoji ir septintoji). Į pirmą grupę (n=40) pateko daugiausia (95 proc.) griuvimus patyrusių asmenų. Daugumą jų (70 proc.) sudarė moterys, kurios pasižymėjo mažesne galūnių raumenų mase (18,27 kg), mažesniu KMT šlaunikaulio srityje (0,840 g/cm^2), mažesne vitamino D koncentracija kraujyje (12,2 ng/ml) ir didžiausia iš suformuotų grupių parathormono koncentracija kraujyje (73,02 ng/ml). Septintos grupės daugumą sudarė negriuvę per pastaruosius metus vyrai (80 proc. nepatyrusių griuvimų), kurių vitamino D koncentracija kraujyje buvo didžiausia (28,65 ng/ml), o parathormono – mažiausia (45,19 ng/ml). Šių vyrų KMT šlaunikaulio srityje (1,031 g/cm^2), galūnių raumenų masė buvo vieni iš didžiausių, lyginant su kitomis grupėmis.

Genetiniai tyrimai buvo atlikti 73 moterims, iš kurių 28 moterys sirgo sunkia osteoporoze po menopauzės (amžiaus vidurkis 74,12±6,43 metų). Kontrolinę grupę sudarė 45 moterys, nesergančios osteoporoze ir atitinkančios pagrindinę grupę pagal amžių (amžiaus vidurkis 72,9±5,95 metų, p=0,424). Nustatyta, kad 9 (32,1 proc.) moterų sergančių sunkia osteoporoze ir 22 (48,9 proc.) kontrolinės grupės moterų turėjo *VDR Bsm*I *bb* genotipą. *VDR Bsm*I *Bb* genotipas buvo nustatytas 14 (50 proc.) moterų sergančių sunkia osteoporoze ir 17 (37,8 proc.) kontrolinės grupės moterų. Mūsų tyrimo duomenimis *VDR Bsm*I *BB* genotipas nustatytas tik 5 (17,9 proc.) sunkios osteoporozės grupės moterų ir 6 (13,3 proc.) kontrolinės grupės moterų. *VDR Bsm*I genotipai statistiškai reikšmingai nesiskyrė tarp moterų sergančių sunkia osteoporoze ir kontrolinės grupės moterų.

Nustatėme, kad sergančių sunkia pomenopauzine osteoporoze moterų stuburo juosmeninės srities kaulų mineralų tankis buvo didesnis esant *VDR* geno *Bsm*I *BB* genotipui, nei esant *bb* ar *Bb* genotipams. Esant *VDR* geno *Bsm*I *bb* genotipui, sunkia pomenopauzine osteoporoze sergančių moterų šlaunikaulio kaklo kaulų mineralų tankis vidutiniškai stipriai koreliavo su vitamino D koncentracija kraujyje.

Išvados

1. Vitamino D trūkumas nustatytas daugumai tirtų senyvo amžiaus žmonių: 72,2 proc. moterų ir 65,6 proc. vyrų. Mažiausia vitamino D koncentracija kraujyje nustatyta 80 metų ir vyresniems vyrams ir moterims. Esant vitamino D koncentracijai kraujyje mažesnei nei 20 ng/ml abiejų lyčių asmenų kaulų mineralų tankis, vyrų raumenų masė ir moterų fizinis pajėgumas yra mažesni, negu esant pakankamai vitamino D koncentracijai.

2. Senyvame amžiuje vitamino D koncentracija kraujyje statistiškai reikšmingai vidutiniškai koreliuoja su rankų raumenų jėga moterims, su raumenų mase vyrams ir su viso kūno kaulų mineralų tankiu abiejų lyčių asmenims. Maža raumenų masė ir jėga, mažas eisenos greitis yra reikšmingai susiję su griuvimais. Klasterinės analizės rezultatai parodė, kad daugiausiai griuvusiųjų grupėje yra moterys, kurių vitamino D koncentracija kraujyje yra maža (12,2 ng/ml), maža galūnių raumenų masė ir mažas šlaunikaulio bendras kaulų mineralų tankis (0,842 g/cm^2). Mažiausiai griuvusiųjų grupėje yra vyrai, kurių vitamino D koncentracija kraujyje yra artima optimaliai (28,65 ng/ml), didelė galūnių raumenų masė ir didelis šlaunikaulio kaulų mineralų tankis (1,031 g/cm^2).

3. Sergančių sunkia pomenopauzine osteoporoze moterų stuburo juosmeninės srities kaulų mineralų tankis yra didesnis esant *VDR* geno *Bsm*I *BB* genotipui, nei esant *bb* ar *Bb* genotipams. Esant *VDR* geno *Bsm*I *bb* genotipui, sunkia pomenopauzine osteoporoze sergančių moterų šlaunikaulio kaklo kaulų mineralų tankis vidutiniškai stipriai koreliuoja su vitamino D koncentracija kraujyje.

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2. Strazdiene V. Relationship between vitamin D and cardiometabolic risk factors among community dwelling persons. (Oral presentation at European Calcified Tissue Society PhD training courses, September 1-4, 2011, Ljubljana, Slovenia).

3. Strazdiene V, Alekna V, Tamulaitiene M, Mastaviciute A. Relationship of vitamin D and parathyroid hormone with obesity in community dwelling women. Osteoporos Int 2012;23(Suppl.2):S208-S209. (Poster presentation at European Congress on Osteoporosis and Osteoarthritis, ECCEO12-IOF, March 21-24, 2012, Bordeaux, France).

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CURRICULUM VITAE

First name: Vaidilė

Surname: Strazdienė

E-mail: vaidile.strazdiene@osteo.lt

Education:

1998–2005	Vilnius University, Faculty of Medicine
2006–2008	Residency of Family Medicine, Vilnius University, Qualification of Family Physician
2008–2012	PhD student at State Research Institute Centre for Innovative Medicine and Vilnius University

Work experience:

From 2006	– Family Physician at A. Kazakauskienės family care center
From 2012	– Family Physician at Baltic American Medical and Surgical Clinic
From 2013	– Physician at National Osteoporosis Center

Field of scientific interests:

Ageing, bone metabolic diseases, Vitamin D, falls