УДК 612.825

DOI: http://dx.doi.org/10.15674/0030-598720232

Serum vitamin D in patients with benign, primary malignant and metastatic bone tumors

O. V. Drobotun [1, 2], M. K. Ternovy [2], M. M. Kolotilov [3]

[1] CNE «Kyiv City Clinical Hospital No. 3» of the Kyiv City Council, Ukraine
[2] R. E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of the NAS of Ukraine. Kyiv
[3] Institute of Nuclear Medicine and Diagnostic Radiology of the National Academy of Medical Sciences of Ukraine. Kyiv

Participant in the process of normal bone remodeling is vitamin D, which, in addition, has anti-inflammatory (anti-cytokine), anti-proliferative and anti-tumor effects. Objective of the study is to assess the level of 25-hydroxyvitamin D_3 concentration in blood serum before the start of treatment in patients with benign, primary malignant and metastatic bone tumors, taking into account polymorbidity. Materials and methods. The following patients were included in the study: 21 patients with benign pelvic bone tumors; 52 patients with malignant tumors of the bones of the pelvis and lower limbs; 52 patients with metastatic tumors of the bones of the pelvis and lower limbs. The control group consisted of 22 practically healthy volunteers without chronic diseases. The content of vitamin D was determined by the immunochemiluminescence method. The results. The content of vitamin D in blood serum in patients with benign bone tumors is in the range from 22.4 to 29.6 ng/ml, with primary malignant tumors — from 7.8 to 15.9 ng/ml, with metastatic ones — from 13.8 to 15.5 ng/ml. There are no statistically significant differences between the histotypes of primary malignant bone tumors ($p > 0.05$). Conclusions. Polymorbidity statistically significantly increases vitamin D deficiency in patients with osteogenic sarcoma and patients with metastatic bone tumors ($p < 0.05$). According to the national classification of vitamin D content, patients with benign bone tumors have a suboptimal level of vitamin D, while patients with primary malignant and metastatic bone tumors have vitamin D deficiency.

Вітамін D є важливим регулятором процесу ремоделювання кісток і, крім цього, має протизапальну (антицитокіновy), антипроліферативну та протипухлинну дії. Мета. Оцінити рівень 25-гідроксивітаміну D_3 у сироватці крові хворих на доброякісні та первинні злоякісні пухлини й метастатичні ураження кісток з урахуванням поліморбідності. Методи. У дослідження включено: 21 пацієнт (вік 41–59 років) із доброякісними пухлинами кісток таза; 52 (вік 38–60 років) — зі злоякісними пухлинами кісток таза та нижніх кінцівок; 52 (вік 38–57 років) із метастатичними ураженнями кісток таза та нижніх кінцівок. Серед осіб із первинними злоякісними пухлинами та метастатичними ураженнями кісток майже всі мали супутні захворювання. Контрольна група — 22 волонтери без хронічних захворювань. Вміст вітаміну D визначали імунохемілюмінесцентним методом. Результати. Вміст вітаміну D у сироватці крові пацієнтів із доброякісними пухлинами кісток дорівнював 22,4–29,6 нг/мл, із первинними злоякісними — 7,8–15,9 нг/мл, метастатичними ураженнями — від 13,8–15,5 нг/мл. Значущої відмінності рівнів вітаміну D у хворих на різні види первинних злоякісних пухлин не встановлено. У разі первинних злоякісних пухлин рівень вітаміну D був суттєво нижчим, ніж в осіб із доброякісними пухлинами. У жодного з хворих на ангіосаркому, хондросаркому або саркому Юїнга не встановлено достатній рівень вітаміну D. За умов коморбідних захворювань збільшувався дефіцит вітаміну D, але статистично значущі відмінності визначено лише для пацієнтів з остеогенною саркомою та метастатичними ураженнями кісток. Висновки. Практично в 100 % пацієнтів із первинними злоякісними пухлинами (12 гістотипів) і метастатичними ураженнями (4 гістотипи) кісток таза та нижніх кінцівок виявлено дефіцит вітаміну D у сироватці крові, із доброякісними пухлинами (6 гістотипів) — субоптимальний його рівень. За умов коморбідних захворювань установлено суттєво більший дефіцит вітаміну D у пацієнтів з остеогенною саркомою та метастатичними ураженнями кісток. Ключові слова. Вітамін D, пухлини кісток, метастатичні ураження кісток, поліморбідність.

Key words. Vitamin D, blood serum, bone tumors, polymorbidity

Introduction

Vitamin D is a general term used to refer to vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Calcidiol (25(OH)D) is the main circulating form of vitamin D and reflects its reserves in the body. The half-life of calcidiol is 14 days. The biological action of vitamin D is realized by the active form of the hormone, calcitriol (1,25(OH)2D3). Its classic effects are determined by calcium exchange; parathyroid hormone synthesis; phosphate/calcium exchange in the kidneys; differentiation and functioning of osteoblasts and osteoclasts. The non-classic effects of calcitriol include antiproliferative, antibacterial, anti-inflammatory (anticytokine), immunomodulatory, normoglycemic (insulin), antidepressant, analgesic, anabolic, lipolytic, organoprotective, hypotensive, as well as regulation of apoptosis and angioneogenesis [1].

The activity of calcidiol (25OHD3) is 1000 times lower than that of calcitriol, but the effects are similar, since the concentration of calcidiol in blood serum is higher — 30 μg/l [2]. It is this metabolite that is most evidently associated with indicators of bone tissue health and is the only informative biochemical marker of vitamin D status in the human body. Taking vitamin D supplements increases 25(OH)D levels to a greater extent [1, 2].

The anti-proliferative, anti-apoptotic and anti-neoangiogenic effects of 25(OH)D make it possible to consider vitamin D as a steroid hormone with oncostatic and oncoprophylactic properties. Vitamin D deficiency has been shown to be associated with an increased risk of cancer through up-regulation of tumor-associated gene expression [3], with a higher incidence of skeletal events and a worse prognosis; high mortality in breast and prostate cancer patients [4]. The effect of vitamin D on bone tumor growth is due in part to increased bone remodeling, but also to a direct effect of vitamin D on cancer cells. In particular, vitamin D has been shown to directly regulate cell proliferation, differentiation, and apoptosis in many tissues, including malignant tumors [5]. Based on this, studies on the determination of vitamin D content in blood serum in patients with primary malignant tumors and metastatic bone lesions [6] without taking into account polymorbidity [7] are considered quite logical.

Purpose: to evaluate the level of 25-hydroxyvitamin D_3 concentration in blood serum of patients with benign and primary malignant tumors and metastatic bone lesions, taking into account polymorbidity.

Material and methods

The study involved the following groups of patients:

– 1st (control) — 22 practically healthy volunteers without chronic diseases aged 36 to 55 years;

– 2nd — 21 individuals with benign pelvic bone tumors, age from 41 to 59 years before treatment;

– 3rd — 52, with malignant tumors of the bones of the pelvis and lower limbs, age from 38 to 60 years before treatment;

– 4th — 52, with metastatic lesions of the bones of the pelvis and lower limbs, age from 38 to 57 years before treatment. The study was conducted in Kyiv.

The criteria for the inclusion of patients in the study were as follows: age from 36 to 60 years, absence of osteoporosis and pain syndrome, normal function of the kidneys (the permissible level of exceeding the upper limit of the reference values of creatinine is not more than 2.5) and the liver (biochemical indicators of bilirubin, ALT, AST are not greater more than 2.5 times the upper limit of the norm), the general somatic status according to the Karnovsky scale is not lower than 80 %; body mass index of 18.5–25 kg/m²; polymorbidity

Patients of the 3rd and 4th groups had such comorbidities as arterial hypertension, ulcer disease, osteoarthritis, arthritis, diabetes 2, cholecystitis, coronary atherosclerosis, coronary heart disease, consequences of myocardial infarction and ischemic stroke. Within the methodology [8], polymorbidity was classified by the number of clinically diagnosed diseases: cancer +1; cancer +3. Among the examined, there were practically no persons with primary malignant tumors and metastatic bone lesions without concomitant diseases.

Criteria for excluding patients from the study: severe condition (Karnovsky score lower than 50 %), mental illness in the history, signs of kidney or liver failure (ALT/AST level over 100 units/l; creatinine over 220 μmol/l), low hematological indicators (hemoglobin lower than 90 g/l, initial number of leukocytes less than 3,000, platelets less than 50,000 in peripheral blood), active infectious process; heart rhythm disturbances, use of narcotic analgesics for pain relief, routine intake of food supplements with vitamin D or drugs that affect bone metabolism (calcium, parathyroid hormone analogues or bisphosphonates).

The diagnosis was established on the basis of clinical examination, history, radiological examinations (x-rays, magnetic resonance imaging, computed tomography, etc.) and histopathological findings.

The content of vitamin 25(OH)D (25-hydroxycalciferol) in blood serum was determined by the immunochemiluminescence method on the ARCHITECT 25-OH Vitamin D Controls automatic analyzer. Detection limit — 2.1 ng/ml, intra-assay variation coefficient — 5.2 %, inter-assay variation coefficient — less than 7 %. Patients were stratified (in addition to the study design) according to the classification of vitamin D content [9]: deficiency — less than 20 ng/ml (50 nmol/l), suboptimal level — 20–30 ng/ml (50–75 nmol/l), optimal (target status) — 30–50 ng/ml (75–125 nmol/l), high content — 50–100 ng/ml (125–250 nmol/l), dangerous level — more than 100 ng/ml (250 nmol/l). Blood was taken on an empty stomach at 7 a.m., before diagnostic procedures and taking medications.

All patients participated in the study after signing informed consent for planned clinical, radiological, laboratory and therapeutic measures. The study was conducted in accordance with the principles of bioethics set forth in the Helsinki Declaration of the World Medical Association «Ethical Principles of Medical Research Involving Humans» and the «General Declaration on Bioethics and Human Rights» (UNESCO), reviewed and approved at the meeting of the Medical Ethics Commission of the Communal Non-Profit Establishment Kyiv Clinical Hospital No. 3 (Protocol No. 3 16.06.2023).

Statistical processing of the material was carried out using methods of variational statistics. Arithmetic mean (C), root mean square (standard) error, and arithmetic mean (m) values were calculated. Differences in mean values in pairwise comparisons, assessed by Student's t-test, were considered statistically significant in $p < 0.01$.

Results and their discussion

The results of determining the content of vitamin D in the blood serum of patients with benign and primary malignant tumors, metastatic bone lesions are presented in Tables 1, 2 and 3.

According to the domestic classification of vitamin D content [9], suboptimal vitamin D levels were found in patients with benign bone tumors, and a deficiency in primary malignant tumors and metastatic lesions. Significant differences in vitamin D levels were found between patients with primary malignant tumors and metastatic bone lesions compared to cases of benign tumors. In particular, patients with primary malignant tumors had significantly lower vitamin D levels than those with benign tumors. None of the patients with angiosarcoma, chondrosarcoma, or Ewing's sarcoma had adequate levels of vitamin D. This indicates the possibility of a relationship between low vitamin D levels and the presence or progression of primary malignant tumors and metastatic bone lesions.

The study showed that under the conditions of comorbid diseases, vitamin D deficiency increases, but statistically significant differences were established only for patients with osteogenic sarcoma and metastatic bone lesions ($p < 0.05$).

Discussion

The results of the study confirm vitamin D deficiency in patients with primary malignant and meta-

Table 1

The content of vitamin D in blood serum in patients with benign and primary malignant bone tumors

Tumor classification	Number of patients	Vitamin D content, ng/ml
Benign tumors		
Aneurysmal bone cyst	5	23.5 ± 2.1
Giant cell tumor of the bone	4	24.1 ± 2.3
Osteoma	3	27.2 ± 2.4
Chondroblastoma	3	28.7 ± 2.3
Osteoblastoma	3	29.6 ± 2.3
Leiomyoma	3	22.4 ± 1.9
Malignant tumors		
Chondrosarcoma	9	9.8 ± 1.2
Osteogenic sarcoma	8	13.6 ± 1.4
Ewing's sarcoma	6	8.5 ± 1.1
Paraosteal osteosarcoma	5	9.2 ± 1.2
Fibrosarcoma	4	10.1 ± 1.1
Malignant lymphoma (primary non-Hodgkin's lymphoma)	4	15.9 ± 1.7
Solitary plasmacytoma of bone	3	14.7 ± 1.6
Malignant giant cell bone tumor	3	12.4 ± 1.3
Angiosarcoma	3	7.8 ± 0.9
Periosteal osteosarcoma	3	8.3 ± 0.9
Adamantinoma	2	11.2 ± 1.1
Epithelioid hemangioendothelioma	2	9.6 ± 1.1

Table 2

Vitamin D content in blood serum of patients with metastatic bone lesions

Primary focus	Number of patients	Vitamin D content, ng/ml
Prostate cancer	18	13.8 ± 1.5
Breast cancer	15	14.4 ± 1,6
Lung cancer	11	15.5 ± 1.3
Kidney cancer	8	14.1 ± 1.4

Table 3

Dependence of vitamin D content (ng/ml) in blood serum of patients determined by polymorbidity

Tumor	Number of patients (cancer +1) + (cancer +3)	Polymorbidity	
		cancer +1	cancer +3
Primary malignant tumors			
Chondrosarcoma	5 + 4	11.2 ± 0.8	8.4 ± 0.9
Osteogenic sarcoma	4 + 4	17.1 ± 1.2	10.1 ± 0.9
Ewing's sarcoma	3 + 3	8.7 ± 0.8	7.3 ± 0.8
Metastatic tumors			
Prostate cancer	8 + 10	15.1 ± 1.1	12.5 ± 1.1
Breast cancer	7 + 8	16.2 ± 1.1	12.6 ± 0.9
Lung cancer	5 + 6	17.3 ± 1.2	13.7 ± 1.1
Kidney cancer	3 + 5	17.2 ± 1.1	11.1 ± 0.9

static bone tumors on a larger number of histological types of tumors on the example of the northern latitude of the city of Kyiv (50°27′ north latitude).

For comparison: according to the most representative data [6], the vitamin D content in the blood serum of 32 patients with bone metastases is on average 13.9 ng/ml (without specifying the primary focus).

Determination of vitamin D content in blood serum has certain limitations that must be taken into account. The levels of vitamin D found in our patients can only be compared with those of people who live in latitudes comparable in terms of the ultraviolet index, for example, in Paris (48°51′ N), Seattle (47°37′), Calgary (51° 3′), Vancouver (49°15′). The full range of reference values for 25(OH)D is not optimized, its upper limit is not defined (there are no reliable biomarkers for determining vitamin D levels for non-classical effects, which should be higher than bone levels) [10–12]. Furthermore, there is currently no international consensus on the specific serum 25(OH) D level that should be considered insufficient or deficient [11, 12]. According to the dietary norms of calcium and vitamin consumption of the US Institute of Medicine, the classification of vitamin D content in blood serum is as follows: the risk of deficiency is less than 12 ng/ml, the risk of insufficient intake is 12–19 ng/ml, and sufficient intake is 20–50 ng/ml [13].

It stands to mention that using standard tests it is impossible to distinguish between 25(OH)D_3 and 3-epi-25(OH)D_3 molecules in blood [14]. Therefore, the obtained values of 25(OH)D_3 can be overestimated by 0.1–4.5 ng/ml due to 3-epi-25(OH)D_3.

Issues related to the impact of a low level of vitamin D on the increased risk of developing cancer and various pathological processes in the body and death are being analyzed [15]. It is known that this nutrient suppresses the process of glycolysis, which is necessary for tumor cells for energy balance, growth and survival. By blocking glycolytic enzymes, vitamin D significantly reduces glucose consumption, activates apoptosis, thus reducing the vital activity of cancer cells [10]. Insufficiency/deficiency of vitamin D was determined in the majority of patients with newly detected breast cancer. Deficiency or insufficiency of vitamin D may be pathophysiologically related to the development or progression of the disease [4].

Bone metastases have devastating consequences, leading to pathological fractures, chronic pain syndrome, life-threatening hypercalcemia and nerve compression syndromes, significantly reducing the quality of life. An increase in the level of polymorbidity is associated with a decrease in X-ray density and an increase in the heterogeneity of cancellous and compact bones (regularity is reliable, $p < 0.01$) in a number of groups: practically healthy individuals, patients with benign tumors, malignant tumors, and metastatic lesions [16]. In reality, all malignant neoplasms can metastasize first to the bone marrow.

Most often, this is characteristic of breast and prostate cancer, lung and kidney cancer. And bone metastasis is a late manifestation of metastasis from the primary focus of these neoplasms to the bone marrow [17].

Conclusions

Virtually 100 % of patients with primary malignant tumors (12 histotypes) and metastatic lesions (4 histotypes) of the bones of the pelvis and lower limbs had vitamin D deficiency in blood serum, with benign tumors (6 histotypes), its suboptimal level.

Under the conditions of comorbid diseases, a significantly greater deficiency of vitamin D ($p < 0.05$)

was established in patients with osteogenic sarcoma and metastatic bone lesions.

Conflict of interest. The authors declare no conflict of interest.

References

1. Lopez, A. G., Kerlan, V., & Desailloud, R. (2021). Non-classical effects of vitamin D: Non-bone effects of vitamin D. *Annales d'endocrinologie, 82*(1), 43–51. https://doi.org/10.1016/j.ando.2020.12.002
2. Rondanelli, M., Moroni, A., Zese, M., Gasparri, C., Riva, A., Petrangolini, G., Perna, S., & Mazzola, G. (2023). Vitamin D from UV-irradiated mushrooms as a way for Vitamin D supplementation: a systematic review on classic and nonclassic effects in human and animal models. *Antioxidants (Basel, Switzerland), 12*(3), 736. https://doi.org/10.3390/antiox12030736
3. Feng, Q., Zhang, H., Dong, Z., Zhou, Y., & Ma, J. (2017). Circulating 25-hydroxyvitamin D and lung cancer risk and survival: A dose-response meta-analysis of prospective cohort studies. *Medicine, 96*(45), e8613. https://doi.org/10.1097/MD.0000000000008613
4. Wu, X., Hu, W., Lu, L., Zhao, Y., Zhou, Y., Xiao, Z., Zhang, L., Zhang, H., Li, X., Li, W., Wang, S., Cho, C. H., Shen, J., & Li, M. (2019). Repurposing vitamin D for treatment of human malignancies via targeting tumor microenvironment. *Acta pharmaceutica Sinica. B, 9*(2), 203–219. https://doi.org/10.1016/j.apsb.2018.09.002
5. Chandler, P. D., Chen, W. Y., Ajala, O. N., Hazra, A., Cook, N., Bubes, V., Lee, I. M., Giovannucci, E. L., Willett, W., Buring, J. E., Manson, J. E., & VITAL Research Group (2020). Effect of Vitamin D_3 Supplements on Development of Advanced Cancer: A Secondary Analysis of the VITAL Randomized Clinical Trial. *JAMA network open, 3*(11), e2025850. https://doi.org/10.1001/jamanetworkopen.2020.25850.
6. Horas, K., Maier, G., Jakob, F., Maus, U., Kurth, A., Jakuscheit, A., Rudert, M., & Holzapfel, B. M. (2017). High Prevalence of Vitamin D deficiency in patients with bone tumors. *Cancer investigation, 35*(8), 562–568. https://doi.org/10.1080/07357907.2017.1351985
7. Williams, G. R., Deal, A. M., Lund, J. L., Chang, Y., Muss, H. B., Pergolotti, M., Guerard, E. J., Shachar, S. S., Wang, Y., Kenzik, K., & Sanoff, H. K. (2018). Patient-reported comorbidity and survival in older adults with cancer. *The oncologist, 23*(4), 433–439. https://doi.org/10.1634/theoncologist.2017-0404
8. Siembida, E. J., Smith, A. W., Potosky, A. L., Graves, K. D., & Jensen, R. E. (2021). Examination of individual and multiple comorbid conditions and health-related quality of life in older cancer survivors. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation, 30*(4), 1119–1129. https://doi.org/10.1007/s11136-020-02713-0
9. Chekman, I. S., Gorchakova, N. A., Berezhniy, V. V., Davydiuk, A. V., & Roman'ko, M. R. (2017). Pharmacology of vitamin D. *Modern pediatrics. Ukraine,* (2), 28–36. https://doi.org/10.15574/SP.2017.82.28 (in Ukrainian)
10. Horas, K., van Herck, U., Maier, G. S., Maus, U., Harrasser, N., Jakob, F., Weissenberger, M., Arnholdt, J., Holzapfel, B. M., & Rudert, M. (2020). Does vitamin D deficiency predict tumour malignancy in patients with bone tumours? Data from a multi-center cohort analysis. *Journal of bone oncology, 25*, 100329. https://doi.org/10.1016/j.jbo.2020.100329
11. Maier, G. S., Horas, K., Kurth, A. A., Lazovic, D., Seeger, J. B., & Maus, U. (2015). Prevalence of Vitamin D deficiency in patients with bone metastases and multiple myeloma. *Anticancer research, 35*(11), 6281–6285.
12. Maier, G. S., Weissenberger, M., Rudert, M., Roth, K. E., & Horas, K. (2021). The role of vitamin D and vitamin D deficiency in orthopaedics and traumatology-a narrative overview of the literature. *Annals of translational medicine, 9*(11), 942. https://doi.org/10.21037/atm-21-779
13. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium, Ross, A. C., Taylor, C. L., Yaktine, A. L., & Del Valle, H. B. (Eds.). (2011). *Dietary Reference Intakes for Calcium and Vitamin D*. National Academies Press (US).
14. Berger, S. E., Van Rompay, M. I., Gordon, C. M., Goodman, E., Eliasziw, M., Holick, M. F., & Sacheck, J. M. (2018). Investigation of the C-3-epi-25(OH)D3 of 25-hydroxyvitamin D_3 in urban schoolchildren. *Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme, 43*(3), 259–265. https://doi.org/10.1139/apnm-2017-0334
15. Segal, E., Felder, S., Haim, N., Yoffe-Sheinman, H., Peer, A., Wollner, M., Shen-Or, Z., & Ish-Shalom, S. (2012). Vitamin D deficiency in oncology patients--an ignored condition: impact on hypocalcemia and quality of life. *The Israel Medical Association journal : IMAJ, 14*(10), 607–612.
16. Ternovoi, N. K. , Kolotilov, N. N. , Drobotun, O. V., Tuz, E. V., Ulyanchich, N. V., & Ternitskaya, Yu. P. (2019). Textural analysis of computer tomographic images of bone tissues: heterogeneity as an indicator of osseointegration (preliminary message). *Radiation diagnostics, radiation therapy*, (1), 43-50. Retrieved from http://nbuv.gov.ua/UJRN/ldlt_2019_1_7
17. Jayarangaiah, A., Kemp, A. K., & Theetha Kariyanna, P. (2022). Bone Metastasis. In *StatPearls*. StatPearls Publishing.

The article has been sent to the editors 01.06.2023

SERUM VITAMIN D IN PATIENTS WITH BENIGN, PRIMARY MALIGNANT AND METASTATIC BONE TUMORS

O. V. Drobotun [1,2], M. K. Ternovy [2], M. M. Kolotilov [3]

[1] CNE «Kyiv City Clinical Hospital No. 3» of the Kyiv City Council, Ukraine

[2] R. E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of the NAS of Ukraine. Kyiv

[3] Institute of Nuclear Medicine and Diagnostic Radiology of the National Academy of Medical Sciences of Ukraine. Kyiv

✉ Oleg Drobotun, MD, PhD in Traumatology and Orthopaedics: olegdrobotun@gmail.com

✉ Mykola Ternovy, MD, Prof. in Traumatology and Orthopaedics: pr.n.terno@gmail.com

✉ Mykola Kolotilov, Prof. in Biol. Sci.: kolotiloff48@gmail.com