Original article

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Evaluation of the efficacy of combined vitamin D_3 and K_2 therapy in reducing implant-associated complication risk and improving spinal fusion stability

Oleksii S. Nekhlopochyn [1], Iryna G. Vasylieva [2], Nataliia G. Chopyk [2], Vadim V. Verbov [3], Ievgen V. Cheshuk [3], Milan V. Vorodi [3]

[1] Spine Surgery Department, Romodanov Neurosurgery Institute, Kyiv, Ukraine
[2] Neurobiochemistry Department, Romodanov Neurosurgery Institute, Kyiv, Ukraine
[3] Restorative Neurosurgery Department, Romodanov Neurosurgery Institute, Kyiv, Ukraine

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Address for correspondence: *Oleksii S. Nekhlopochyn, Spine Surgery Department, Romodanov Neurosurgery Institute, 32 Platona Maiborody st., Kyiv, 04050, Ukraine, e-mail: AlexeyNS@gmail.com*

In the last decade, the use of implants in spinal surgery has significantly increased, particularly interbody devices and transpedicular fixators. This trend has necessitated refining approaches aimed at preventing intra- and postoperative complications. A key factor influencing the effectiveness of stabilization procedures is bone mineral density (BMD).

Objective: To investigate the relationship among vitamin D levels, BMD, and the incidence of implant-related failures in patients who have undergone stabilization procedures on the spine, as well as to evaluate the role of postoperative correction of vitamin D_3 and K_2 deficiencies in enhancing fixation stability and reducing complication risks.

Materials and Methods: A retrospective single-center cohort study was conducted in specialized departments of Romodanov Neurosurgery Institute NAMS of Ukraine, from January 2023 to December 2024. A total of 250 patients who underwent spinal surgery with the use of transpedicular screws and/or interbody implants were analyzed with respect to their age, sex, body mass index, serum vitamin D (25-(OH)D_3) levels, and BMD (according to computed tomography data). Original grading scales were used to evaluate implant-related complications. Postoperative correction of vitamin D deficiency was carried out using "Solemax®" (vitamin D_3, vitamin K_2, and ω-3 polyunsaturated fatty acids).

Results: A high prevalence of vitamin D deficiency and reduced BMD was recorded among patients undergoing elective stabilization surgeries on the spine. A significant correlation was detected between 25-(OH)D_3 levels and bone tissue status. After 4 months of "Solemax®" administration, all patients achieved reference 25-(OH)D3 levels, indicating the effectiveness of the therapy. In the correction group, an increase in BMD was observed, whereas in the comparison group, BMD values decreased. The incidence of implant-related complications was statistically reduced: the risk of screw loosening decreased by 69.84% over the first 6 months and by 85.06% over one year, while the risk of interbody implant migration declined by 56.2% and 64.7%, respectively.

Conclusions: The stability of spinal fusion is more contingent upon the adaptive response of bone tissue to implantation than on absolute BMD values. The use of a balanced combination of vitamins D_3 and K_2 contributes to enhanced fixation stability and a lower risk of postoperative complications.

Keywords: *spine surgery; bone mineral density; vitamin D deficiency; implant-related complications; spinal fusion stability*

Introduction

Significant advances in scientific and technological progress, along with the implementation of highly effective treatment methods in practical healthcare, have considerably contributed to improving the quality and efficiency of medical care delivery to the population [1]. This trend is particularly evident in the field of surgery, which has seen both an expansion in the range of surgical procedures and an increase in their frequency. According to epidemiological studies, the global number of surgical interventions increased by more than 30% between 2000 and 2012 (from 226.4 to 312.9 million per year) [2]. However, it has also been reported that over 143 million necessary surgical procedures—vital for saving lives or preventing permanent disability—were not performed due to technical, economic, or other constraints [3].

A more pronounced dynamic is observed in spinal surgery, driven by demographic and technological factors as well as lifestyle-related aspects of certain population groups [4]. Technological advancements in spinal surgery over recent decades have significantly increased the use of implants, particularly interbody

constructs and transpedicular fixation devices. This trend reflects not only the refinement of surgical techniques but also the substantial broadening of indications for surgical intervention. In a study by S.S. Rajaee et al., which analyzed trends in spinal stabilization procedures in the United States from 1998 to 2008, a 137% increase in surgeries was noted (from 174,223 to 413,171 procedures, respectively) [5]. The greatest growth in surgical volume was observed among elderly patients, attributed to both the rising number of older individuals and the corresponding need to address degenerative spinal changes. The introduction of advanced fixation techniques has also contributed to the increase in surgeries. This was noted by M.-J. Reisener et al. [6], who reported a significant rise in the use of implants in lumbar spine surgeries. From 2002 to 2011, the number of lumbar spinal fusion procedures grew by 77% in the United States and by 63% in the United Kingdom. The authors cite the adoption of minimally invasive techniques and expanded surgical indications as key drivers of this growth.

An analysis of the publicly available U.S. National Inpatient Sample database revealed that national expenditures for thoracolumbar spinal stabilization procedures (excluding major complications or comorbidities) rose by $7.04 million (44.41%) from 2008 to 2014 [7]. This category of surgical intervention ranks first in economic significance among neurosurgical procedures—total costs exceeding those for craniotomies and endovascular cerebral procedures by a factor of 5.83—and ranks sixth in overall healthcare expenditures across Medicare Severity-Diagnosis Related Groups. According to the authors, this substantial increase is likely driven by a combination of factors, including enhanced understanding of spinal biomechanics, advancements in modern diagnostic techniques, improved surgical technologies and instrumentation, and an increase in average life expectancy.

It is natural that the active implementation of stabilization procedures in practical healthcare is accompanied by the evolution of methods aimed at preventing complications and adverse events, both those arising directly from the surgical intervention and those associated with its long-term outcomes. According to several studies, the application of intraoperative three-dimensional navigation (Image-Guided Navigation) allows for highly accurate placement of pedicle screws, achieving a Grade A rating under the Gertzbein–Robbins classification in up to 99% of cases [8]. This high precision is attributed to the ability to visualize patient anatomy in real time using three-dimensional imaging, thereby significantly reducing the likelihood of malpositioning [9, 10].

By contrast, the accuracy of pedicle screw placement when using traditional two-dimensional fluoroscopy ranges between 70–90%, which increases the risk of screw misplacement, fixation failure, and, in certain cases, damage to critical anatomical structures. Notably, the use of the conventional Free-hand technique results in incorrect transpedicular screw positioning in approximately one out of every six cases [11].

Furthermore, a range of complications unrelated to the surgical technique itself has been documented in spinal stabilization procedures. Quite often, failure to achieve secondary stable spondylosis, interbody implant dislocation, pedicle screw displacement or extraction, and the development of deformity of adjacent segments to the stabilized segments are frequently influenced by patient-specific factors, which complicates treatment strategies and underscores the need for a personalized approach to care [12]. A critical determinant of the success of spinal stabilization is bone mineral density (BMD) [13,14]. Various strategies have been developed to enhance the stability of spinal fixation, employing both localized and systemic methods. Almost the only method of etiotropic therapy of low BMD, vitamin D supplementation emerges as a foundational and broadly applicable intervention. It is favored for its affordability, ease of monitoring, and suitability for long-term outpatient administration. In cases of severe osteoporosis, vitamin D is often integrated into a comprehensive treatment regimen. When used in conjunction with calcium supplements, bisphosphonates, or anabolic agents such as teriparatide, vitamin D has demonstrated favorable clinical outcomes [15,16]. Given the endemic prevalence of vitamin D deficiency in Eastern European populations and its established influence on BMD, investigating the correlation between spinal fusion failure and vitamin D levels—as well as assessing the impact of postoperative vitamin D correction—represents an important area of research for improving the outcomes of spinal stabilization surgeries.

Objective: To investigate the relationship between vitamin D levels, bone mineral density (BMD), and the incidence of spinal fusion failure in patients undergoing spinal stabilization surgery, as well as to assess the role of postoperative correction of vitamin D_3 and K_2 deficiencies in enhancing fixation stability and reducing the risk of complications.

Materials and Methods

Study design

From January 2023 to December 2024, a retrospective monocentric cohort study was conducted at the specialized departments of the Romodanov Institute of Neurosurgery, National Academy of Medical Sciences of Ukraine.

Inclusion Criteria:

- Patients aged 18 to 81 years;
- Underwent stabilization surgery in the thoracolumbar spine using transpedicular screws and/or interbody implants;
- Availability of clinical documentation, including preoperative and postoperative follow-up data, enabling evaluation of fixation stability, implant positioning, and BMD;
- Postoperative dynamic assessment of 25(OH) D levels;
- Signed informed consent for data collection, processing, and publication of generalized results under the condition of confidentiality.

This article contains some figures that are displayed in color online but in black and white in the print edition.

Exclusion Criteria:

- Documented postoperative infectious-inflammatory complications at any time during the follow-up;
- BMD value <50 HU;
- Revision surgeries;
- Improper initial placement of implants (transpedicular screws or PLIF/TLIF cages);
- History of trauma and/or spinal surgery prior to the intervention analyzed in this study;
- Presence of neoplastic processes of any localization or any somatic pathology in the stage of decompensation;
- Persistent psychiatric or behavioral disorders.

Parameters studied:

Baseline clinical parameters included patients' age, sex, and body mass index (BMI).

Vitamin D (25-(OH)D) levels were classified as follows: normal – ≥30 ng/mL, insufficient – 20–29 ng/mL, deficient – <20 ng/mL [17]. If the results were reported in nmol/L, a conversion formula was applied: ng/mL = (nmol/L) ÷ 2.5

Bone mineral density was assessed using computed tomography (CT), which, according to several studies, provides more informative results for the spine than conventional dual-energy X-ray absorptiometry (DEXA) and is more accessible for neurosurgical patients, as it is often performed routinely [18]. Measurements were carried out using the RadiAnt DICOM Viewer software package (Medixant, Poland; version 2023.1, License No. 1860F047) at the level of the middle third of the L1 vertebral body. An ellipsoid region-of-interest (ROI) was drawn to include as much trabecular bone as possible while excluding the cortical shell. BMD values were classified as follows: normal – >120 HU, osteopenia – 80–120 HU, osteoporosis – 50–80 HU, severe osteoporosis – <50 HU [19–21]. Patients with BMD <50 HU were excluded from the study, as such cases typically require specialized surgical techniques (e.g., cannulated screws with polymethylmethacrylate augmentation) or nonsurgical approaches due to a very high risk of complications.

In some cases, preoperative preparation with therapy was conducted in specialized medical institutions.

Age groups for analysis were formed in accordance with the recommendations of the Endocrine Society Clinical Practice Guidelines and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) [22].

Assessment of postoperative complications

Given the lack of a standardized classification in contemporary literature for fixation failure within the "pedicle screw–vertebral body" system—commonly referred to as "screw loosening"—we propose the following grading system based on existing studies [23–26]:

- Grade 0 (no loosening): The screw is visually and clinically stable, with no signs of osteolysis surrounding the screw as confirmed by CT or spondylography.
- Grade 1 (minimal loosening): Slight osteolytic changes around the screw (radiolucency <0.5 mm) observed on spiral CT (SCT); the screw shows slight instability, though clinical symptoms are absent or minimal. No changes are detectable on standard spondylography.
- Grade 2 (moderate loosening): Radiolucency of 0.6–2.0 mm around the screw; intraoperative palpation may reveal screw mobility. Clinically, this may present as mild pain or slight construct instability. Changes are not detectable via spondylography.
- Grade 3 (significant loosening): Radiolucency >2 mm; the screw is clearly unstable and may partially extrude from the bone structure. Clinical manifestations include pain, segmental instability, and functional impairment. Overloading of adjacent implant components may occur. These changes are verifiable on standard radiographs.
- Grade 4 (complete loosening): The screw completely loses fixation and may migrate. Associated with substantial bone defects, possibly resulting in secondary vertebral fracture. Clinically presents with acute pain, spinal instability, or neural compression.
- For the dislocation of interbody cages, we also propose the following classification based on descriptive studies [27–29], assessed via radiography or CT:
- Grade 0: No displacement.
- Grade 1: Mild displacement (<2 mm), with the posterior edge of the cage remaining within the vertebral body and without clinical symptoms.
- Grade 2: Moderate displacement (2–5 mm), with the posterior edge of the cage extending beyond the dorsal margin of the vertebral body, potentially compressing the intervertebral foramen or spinal canal; manifests as localized pain.
- Grade 3: Severe displacement (>5 mm), characterized by clinical signs of neural structure compression and necessitating surgical revision.

The initial evaluation of positioning was performed using standard spondylography. In case of verification ≥Grade 1, spiral computed tomography (SCT) was used for further monitoring. Postoperative vitamin D deficiency correction was administered using "Solemax® 4000" (Vitamin D_3 [cholecalciferol] – 100 mcg [4000 IU], Vitamin K_2 [menaquinone, MK-7] – 100 mcg, ω-3 polyunsaturated fatty acids – 400 mg) or Solemax® 5600 (Vitamin D_3 – 140 mcg [5600 IU], Vitamin K_2 – 100 mcg, ω-3 polyunsaturated fatty acids – 400 mg). Both formulations are manufactured by "Solepharm" LLC (Latvia). Serum 25-(OH)D_3 levels were monitored every two months until normalization was achieved, with follow-up measurements performed every six months thereafter. The frequency of follow-up X-rays or SCTs was determined based on clinical indications.

Statistical Analysis

Statistical analysis was conducted using R software (version 4.0.5, R Foundation for Statistical Computing) in the RStudio development environment (version 1.4.1106).

Results

A total of 250 clinical cases were included in the analysis based on the availability of medical records and postoperative follow-up data provided remotely by patients. Patients were categorized into three groups depending on their need for vitamin D_3 correction (based on 25-(OH)D_3 levels) and actual intake of "Solemax®":

1) No Need for Correction (NNC) – Patients whose vitamin D_3 levels were within the normal range and did not require correction.

2) Solemax® Recommended Dose (SRD) – Patients whose vitamin D3 levels required correction and who received "Solemax®" at the recommended dosage.

3) Needed, but Not Treated (NNT) – Patients identified as needing correction of vitamin D3 levels but who, for various reasons, declined any form of supplementation. This group was included in the analysis as they provided follow-up results of postoperative imaging (including spondylography) and laboratory data.

Vitamin D3 correction in the postoperative period is not governed by any official protocols; thus, all prescriptions were of a recommendatory nature.

Primary data analysis revealed that patients in the NNC group were characterized by a statistically significantly younger age compared to those in the SRD and NNT groups. Additionally, the NNC group demonstrated significantly higher BMD values ($p < 0.001$) than the other groups. No cases of overt osteoporosis were identified, and osteopenia was observed in only 10.5% of cases.

The relatively younger age of patients in the NNC group also influenced the types of surgical interventions performed. Lumbar discectomies with posterior lumbar interbody fusion (PLIF) was the predominant procedure. Isolated transpedicular fixation (TPF) was primarily carried out using minimally invasive techniques in cases of uncomplicated traumatic spinal injuries that required indirect decompression and stabilization. The primary indications for combined PLIF and TPF were unstable spondylolisthesis with radiographic evidence of spondylolysis.

The SRD and NNT groups, whose data were used for further analysis, showed no statistically significant differences in the parameters studied, confirming their comparability and the validity of subsequent analysis. Statistical evaluation of the entire patient cohort enabled the identification of certain associations consistent with existing literature, supporting the robustness of the data collection and analysis methodology.

Of particular note is the observed correlation between BMD, patient age, and sex ***(Fig. 1A)***.

In individuals under the age of 40, predominantly normal bone mineral density (BMD) values were recorded. Among 88 patients in this age group, 63 (71.6%) had BMD values ≥120 HU, 20 (22.7%) had values in the range characteristic of osteopenia, and 5 (5.7%) had values corresponding to osteoporosis. The distribution of data demonstrated moderate variability,

Table 1. Brief characteristics of patient groups

Indicator	Group			P*
	NNC (n=38)	SRD (n=115)	NNT (n=97)	
Sex:				0,1378Δ
men	14 (36,84 %)	43 (37,39 %)	47 (48,45 %)	
women	24 (63,16 %)	72 (62,61 %)	50 (51,55 %)	
Age, years (median):	29 (95 % CI – 26,94–33,58)	51 (95 % CI – 46,98–51,84)	47 (95 % CI – 45,68–51,16)	0,3027#
18–40	32 (84,21 %)	28 (24,35 %)	33 (34,02 %)	0,2299*
41–60	5 (13,16 %)	62 (53,91 %)	42 (43,3) %	
>60	1 (2,63 %)	25 (21,74 %)	22 (22,68 %)	
Body mass index, kg/м2 (median)	24,55 (95 % CI – 22,77–25,01)	24,20 (95 % CI – 23,64–25,15)	25,40 (95 % CI – 24,51–26,13)	0,07307#
Type of surgical intervention:				0,3382*
PLIF	30 (78,95 %)	69 (60 %)	50 (51,55 %)	
TPF	2 (5,26 %)	14 (12,17 %)	18 (18,56 %)	
TPF + PLIF	6 (15,79 %)	32 (27,83 %)	29 (29,9 %)	
BMD, HU (median):	156,65 (95 % CI – 145,72–163,19)	93,90 (95 % CI – 94,11–104,42)	96,10 (95 % CI – 95,56–105,52)	0,4631#
normal	34 (89,47 %)	23 (20 %)	23 (23,71 %)	0,5972*
osteopenia	4 (10,53 %)	62 (53,91 %)	54 (55,67 %)	
osteoporosis	–	30 (26,09 %)	20 (20,62 %)	
25-(OH)D3, ng/ml:	43,53 (95 % CI – 41,21–48,94)	20,68 (95 % CI – 20,35–21,67)	20,09 (95 % CI – 20,42–21,97)	0,9919#
normal	38 (100 %)	–	–	0,4005Δ
insufficient	–	67 (58,26 %)	50 (51,55 %)	
deficient	–	48 (41,74 %)	47 (48,45 %)	

Notes:

PLIF – posterior lumbar interbody fusion; TPF – transpedicular fixation; BMD – bone mineral density; CI – confidence interval.

*Statistical significance of differences between the SRD and NNT groups was calculated; Δ – Pearson's χ^2 test with Yates' continuity correction; #– Wilcoxon rank-sum test with continuity correction; * – Pearson's χ^2 test.*

as indicated by the coefficient of variation (CV = 22.96%), suggesting relative stability in BMD values within this age group despite individual differences. The analysis revealed an almost linear inverse relationship between BMD and age, confirmed by Pearson's correlation coefficient (r = −0.684). Statistically significant sex differences in BMD were found in patients under 40: the median BMD was 149.40 HU (95% confidence interval [CI]: 137.14–154.15) in women and 130.50 HU (95% CI: 117.81–138.42) in men (p = 0.0044).

The 41–60 age group was characterized by a noticeable decline in BMD. In this group, 64.9% of patients had values consistent with osteopenia, 22.8% with osteoporosis, and only 12.3% had normal BMD values. The dispersion of values was also moderate (CV = 20.92%). In contrast to the younger cohort, an inverse trend in BMD relative to sex was observed: women had a median of 91.30 HU (95% CI: 87.14–97.41), while men had a median of 94.90 HU (95% CI: 92.00–102.91); however, the difference was not statistically significant (p = 0.1266). The correlation between bone tissue status and age was also considerably weaker compared to younger patients (r = −0.2614), indicating a diminished age-related dependency of BMD in this group. A visual analysis of the trend lines ***(see Fig. 1A)*** further supported that the age-BMD relationship in men was notably weaker than in women. This may reflect sex-specific dynamics in bone density, potentially associated with differences in metabolic and hormonal factors.

In patients over the age of 60, a similar trend was noted as in younger individuals. The proportion of patients with osteoporosis was 29.6%, with osteopenia—54.2%, and with normal BMD—6.3%. The median values for women and men were 80.30 HU (95% CI: 74.53–85.76) and 96.45 HU (95% CI: 84.75–103.94), respectively, with a statistically significant difference (p = 0.0125).

Based on existing literature, a substantial decrease in BMD in postmenopausal women could have been expected during analysis; however, when interpreting the results, it is important to consider that patients with pronounced manifestations of osteoporosis were not included in the study. The analysis of 25-(OH)D₃ levels by age group revealed a similar trend, albeit with specific nuances ***(Fig. 1B)***. In younger patients (<40 years), higher levels of 25-(OH)D₃ were expectedly recorded. Nevertheless, even within this age group, only 36.36% of patients had normal vitamin D₃ levels, while insufficiency and deficiency were observed in 44.32% and 19.32% of patients, respectively. In the 40–60-year-old age group, the distribution of 25-(OH)D₃ levels was 4.38%, 50.0%, and 45.61%, respectively, and among patients over 60 years of age—2.08%, 43.75%, and 54.17%.

The median 25-(OH)D₃ values across age groups were as follows:

- <40 years: 27.23 ng/mL (15.94–65.28); males—22.97 (95% CI: 24.32–32.62), females—29.32 (95% CI: 29.01–36.79);
- 40–60 years: 20.26 ng/mL (15.15–33.71); males—20.61 (95% CI: 20.34–23.84), females—19.70 (95% CI: 19.73–22.58);
- >60 years: 19.56 ng/mL (15.13–29.79); males—21.24 (95% CI: 18.21–26.86), females—19.38 (95% CI: 18.75–21.08).

The 25-(OH)D₃ levels were low even when accounting for the endemic nature of vitamin D deficiency in Ukraine. However, these findings reflect the status not of the healthy population but of patients with musculoskeletal disorders, particularly spinal conditions. The development and progression of such diseases may be driven by vitamin D deficiency, which has a considerable impact on bone health and metabolism. Conversely, the presence of musculoskeletal pathology that limits mobility likely contributes to reduced sun exposure, thereby impeding adequate cutaneous synthesis of vitamin D. This is further supported by the observation that the variability of 25-(OH)D₃ levels in the younger age group was significantly higher (CV = 43.1%) compared to older age groups (CV = 27.29% and 30.61% for the 40–60 and >60 age groups, respectively). This may indicate greater heterogeneity in the factors influencing vitamin D levels among younger patients, including lifestyle characteristics, dietary habits, and individual metabolic differences.

The correlation between serum 25-(OH)D_3 levels and bone mineral density (BMD) in patients with spinal pathology, as analyzed in our study, follows an approximately linear sigmoidal relationship with asymptotes defined as physiologically acceptable limits ***(Fig. 2)***. The variability in 25-(OH)D_3 levels decreases with increasing severity of osteoporotic changes (37.79% in individuals with normal BMD, 28.78% with osteopenia, and 11.3% with osteoporosis), which is likely underpinned by a pathophysiological basis.

The nature of the analyzed dependency allows for mathematical modeling using a modified Michaelis–Menten saturation function. In this case, a modification is employed to incorporate an asymptotic growth parameter, which corresponds to one of the variants of the four-parameter logistic function. This approach enables the mathematical characterization of nonlinear changes in system parameters by accounting for the baseline level, growth rate, and asymptote. The relationship is described by the following formula:

$$\mathrm{BMD} = a + \frac{(d-a)}{1+e^{-b\,(VitD3-c)}} \quad (1),$$

Where: BMD – radiologically measured bone mineral density, in Hounsfield units (HU);

$VitD_3$ – serum level of 25-hydroxycholecalciferol, in ng/mL;

a (lower asymptote) – baseline BMD level in cases of severe vitamin D deficiency;

d (upper asymptote) – threshold beyond which increasing vitamin D level has no significant effect;

b (slope) – rate of change in BMD relative to vitamin D level;

c (inflection point) – point at which vitamin D has the most effective impact on bone density.

The resulting predictive model produced the following parameter estimates:

a = 78.76 ± 6.18 (p < 0.001), *d* = 155.42 ± 4.16 (p < 0.001), *b* = 0.324 ± 0.077 (p < 0.001), *c* = 24.78 ± 0.77 (p < 0.001).

The mean prediction error was 21.88, indicating a high level of accuracy for modeling biological processes ***(Fig. 3)***.

The next stage of the analysis involved examining the effect of "Solemax®" on serum 25-(OH)D_3 levels. The dynamics of changes, stratified by age categories and taking into account gender, are presented in ***Fig. 4***.

According to initial testing, in the SRD group, 26.92% of patients under the age of 40 had a vitamin D deficiency (11.54% of men and 15.38% of women). A vitamin D insufficiency was recorded in 73.08% of patients (30.77% of men and 42.31% of women). After two months of taking "Solemax®", insufficiency persisted in only 3.85% of patients, while a normal 25-(OH)D_3 level was achieved in 96.15% of patients (42.31% of men and 53.85% of women).

In the 40–60 age group, vitamin D deficiency was detected in 48.44% of patients (14.06% of men and 34.38% of women), and insufficiency in 51.56% (20.31% of men and 31.25% of women). After two months of "Solemax®" administration, insufficiency persisted in 25.0% of patients (equally among men and women), and normalization of the indicator was achieved in 75.0% of patients (21.88% of men and 53.12% of women). Thus, the dynamics of the regression of serum 25-(OH) D_3 insufficiency were somewhat lower compared to younger patients.

Even less pronounced changes were recorded in the age group over 60 years. According to baseline testing, 40% of patients had a vitamin D deficiency (12% of men and 28% of women), while the rest showed insufficiency (28% of men and 32% of women). After two months of taking "Solemax®", insufficiency persisted in 32% of patients (12% of men and 20% of women), while a normal 25-(OH)D_3 level was achieved in 68% of patients (28% of men and 40% of women).

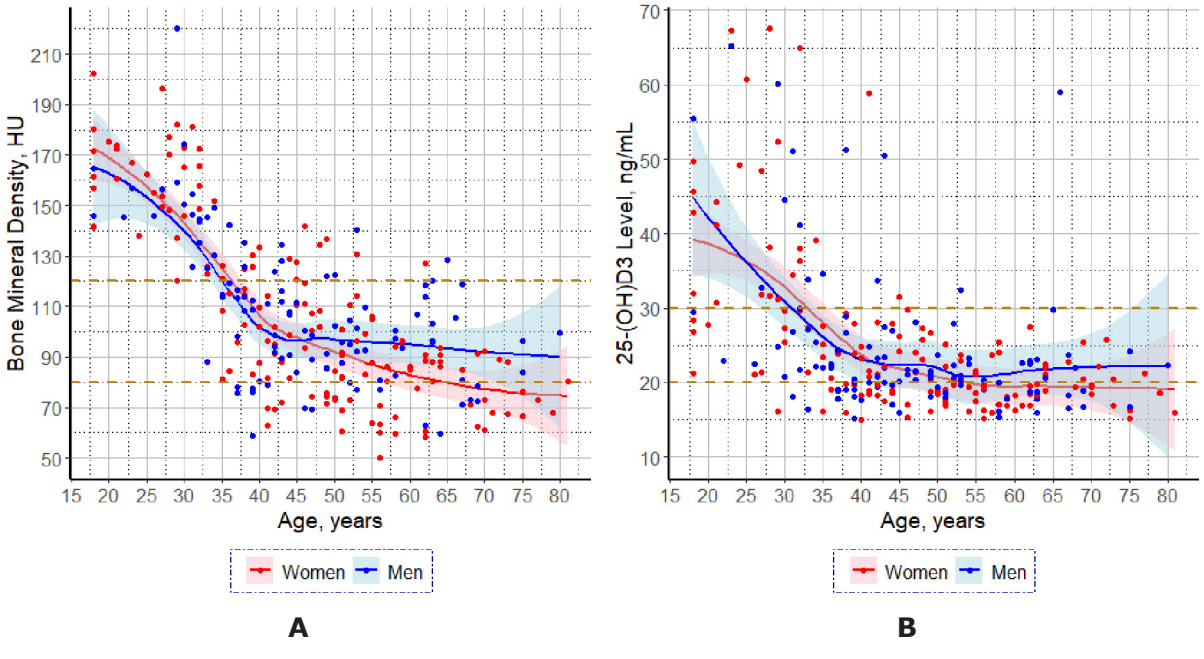

Fig. 1. Association of patient age with bone mineral density (A) and vitamin D3 level (B)

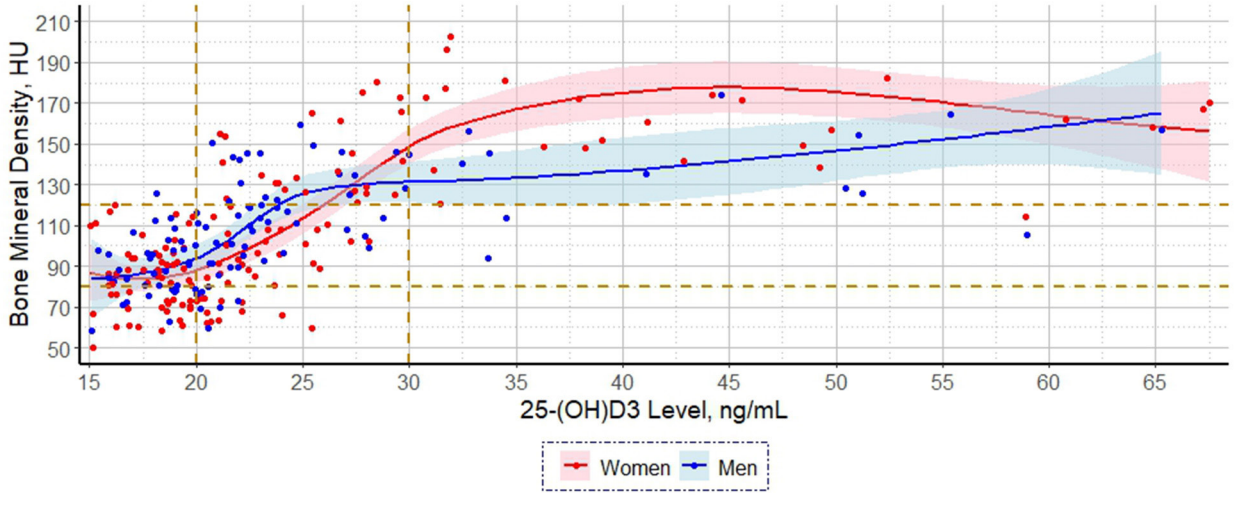

Fig. 2. Relationship between Vitamin D3 level and BMD

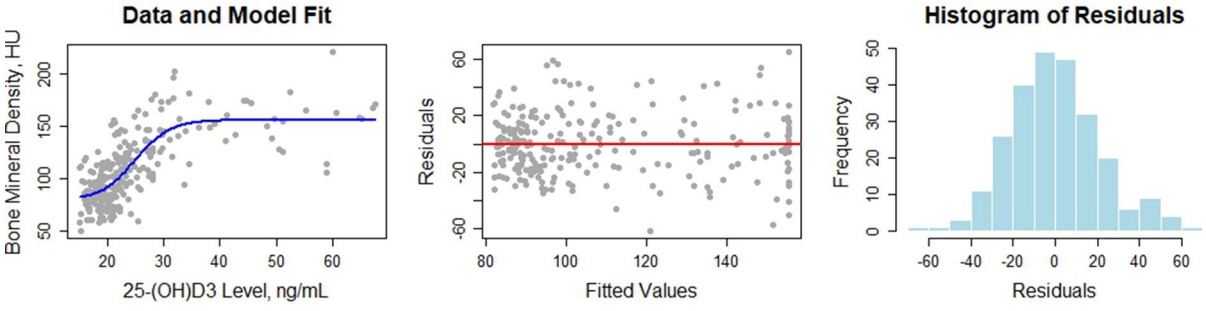

Fig. 3. Graphical evaluation of the model quality characterizing the relationship between vitamin D levels and BMD (explanation provided in the text)

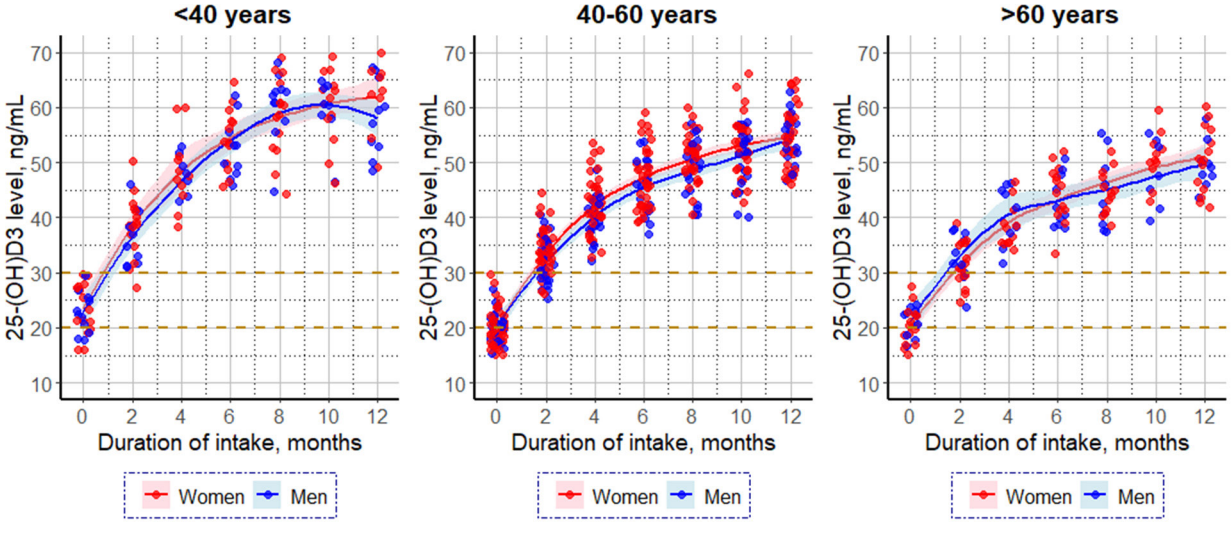

Fig. 4. Dynamics of 25-(OH)D3 levels in blood serum during "Solemax" intake in the postoperative period

After four months of "Solemax®" intake, 25-(OH)D₃ serum levels were within the reference range in all SRD group patients.

Visual assessment of the graphs, as well as the nature of the process under investigation, allow for the approximation of the dynamics of serum 25-(OH)D₃ levels using a logarithmic curve, enabling a mathematical analysis of the quantitative change in this indicator. The model

$$\Delta VitD3 = a + (b \cdot \ln(T)) \quad (2),$$

where – increment in vitamin D level;

T – time (in months, starting from T = 1, to avoid ln (0));

a – the initial increment level, which is a constant;

b – coefficient reflecting the intensity of change in vitamin D increment over time.

Modeling was performed for each age group and sex using equation (2). The analysis results enabled the identification of key patterns. Specifically, comparison of age groups revealed a gradual decrease in both the growth rate (*b*) and the initial growth level (*a*) with increasing age. In males, the initial level (*a*) was higher across all age groups, but it declined more sharply with age. In females, the growth rate (*b*) remained higher than in males across all age groups, indicating a more pronounced dynamic in changes of vitamin D_3 levels.

The slowdown points (T_{25}, T_{10}, T_{50}, T_{75}, T_{95}) remained stable across all age groups for both males and females. This suggests that the process of slowing vitamin D_3 level growth follows a similar pattern regardless of age, albeit with differences in speed and initial level between groups. ANOVA confirmed the significance of the models across all age groups separately for males and females, indicating differences in dynamics between the sexes. However, in older age groups, differences between the individual and the combined model became less significant, suggesting convergence of overall dynamics between males and females with age.

The identified relationships allow the formulation of a general prediction scheme. During the analysis, the following model was used:

$$VitD3_{fin} = a + (b \cdot VitD3_{init}) + (c \cdot \ln(T)) + (d_1 \cdot Gender) + (d_2 \cdot Age), \quad (3)$$

Where: $VitD_{3fin}$ and $VitD_{3init}$ are the target 25-(OH) D_3 serum levels and the initial test values, respectively;

T is the time (in months, 1–12);

Gender is the patient's sex (male = 1, female = 0);

Age is the number of full years at the time of initial testing;

a, b, c, d_1, and *d_2* are model coefficients.

The following results were obtained: *a* = 26.739 – baseline vitamin D level; *b* = 0.471 – weight of the initial vitamin D level; *c* = 11.889 – influence of supplementation duration (ln(T)); *d_1* = –0.452 – sex correction factor; *d_2* = –0.221 – age correction factor.

The adjusted R-squared value was 0.7335, indicating high predictive performance.

Example: Let us calculate the expected serum 25-(OH)D_3 level in a 35-year-old male after 6 months of taking "Solemax®", given an initial vitamin D level of 20 ng/mL:

$VitD_{3fin}$ = 26,739 + 9,42 + 21,32 – 0,452 – 7,735= 49,292.

It is important to note that this model is informative only for patients within the considered category and within 12 months of starting "Solemax®" therapy.

Analysis of 25-(OH)D_3 levels in patients of the NNT group revealed that, at the initial stage of observation, the median level in the 18–40 age group was 22.0 ng/mL (95% CI: 20.6–23.4), in the 41–60 age group – 20.2 ng/mL (95% CI: 19.1–21.3), and in individuals over 60 years old – 18.8 ng/mL (95% CI: 17.4–20.2). A further detailed analysis of the dynamics was not possible due to the lack of regular follow-up testing. However, by the 6-month follow-up point, a portion of patients (49.48%) had provided data, which allowed for a comparative analysis. The 18–40 age group showed a median level of 21.4 ng/mL (95% CI: 19.3–23.5), the 41–60 group – 18.3 ng/mL (95% CI: 16.9–19.6), and the over-60 group – 16.0 ng/mL (95% CI: 14.5–17.6). The decrease was statistically significant for the 41–60 age group (p = 0.03077) and for those over 60 years old (p = 0.01085). In the 18–40 age group, the reduction did not reach statistical significance (p = 0.6331). This dynamic may be explained by lifestyle changes commonly observed in the postoperative period, as well as the natural progression of vitamin D_3 deficiency with age, which is typical in the general population.

The presented data serve as the basis for assessing and interpreting BMD values in patients from the SRD and NNT groups. The analysis of this parameter is associated with several challenges. Firstly, CT scans, which are used to measure BMD, cannot be performed frequently due to the potential burden on the patient from ionizing radiation, as well as financial constraints. Secondly, BMD changes occur slowly, as they reflect long-term processes of bone tissue remodeling. Processes such as bone mass accumulation or the correction of osteopenia or osteoporosis require considerable time before measurable changes can be detected, making their registration difficult. The general dynamics of BMD change are presented in ***Fig. 5***. To provide a more comprehensive picture, the changes are presented as a percentage relative to the baseline value.

The data analysis revealed significant differences in bone tissue changes. Patients in the SRD group demonstrated a gradual increase in BMD, whereas a slight decrease was recorded in the NNT group. Notably, the actual intensity of changes remained minor. The maximum BMD increase by the 12th month of observation was 8.0% from baseline, while the maximum decrease was 5.2%. To assess the influence of various factors on the efficacy of therapy, as well as to determine the statistical significance of the observed dynamics given differences in examination timelines, regression analysis was applied. This approach enables the accommodation of time differences and a more precise quantification of the changes.

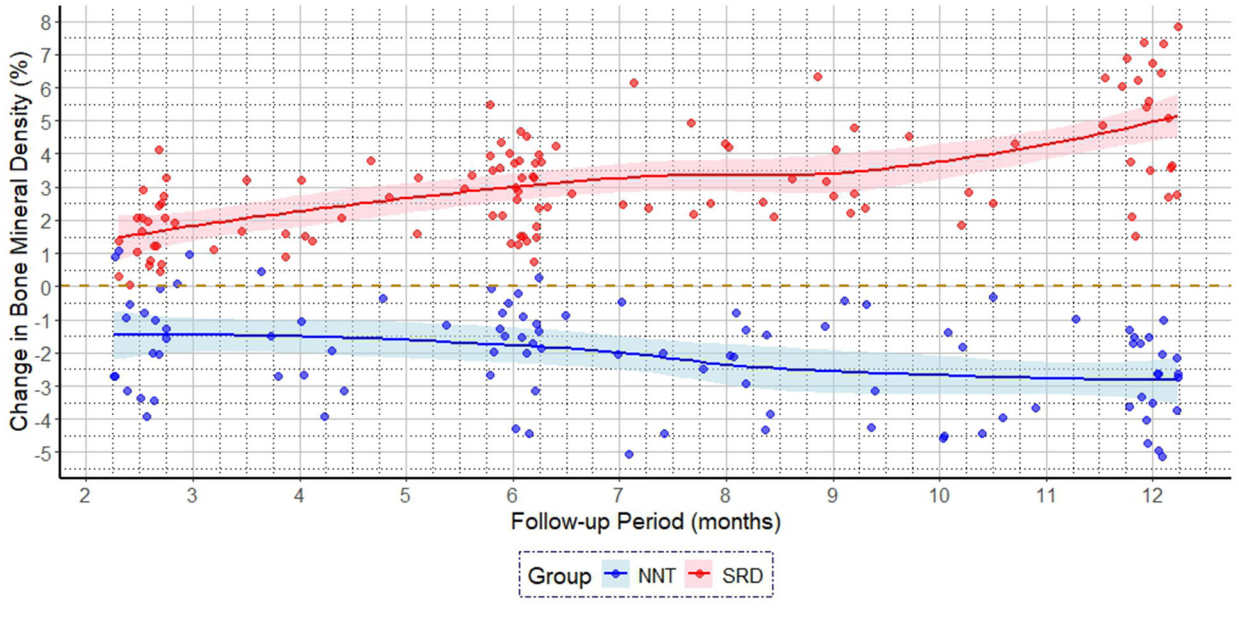

Fig. 5. BMD dynamics in patients. Changes are shown relative to baseline values

It was found that changes in the SRD group are better described by a logistic regression model. When evaluating the dependence of BMD on sex, age, duration of observation, and baseline serum 25-(OH)D_3 levels, it was established that the constructed model effectively describes the phenomenon under study: the adjusted R-squared was 0.6712, and the F-statistic was 59.18 ($p < 0.0001$).

Assessment of the "observation period" factor (coefficient = 1.643, $p < 0.0001$) indicated an exponential nature of the relationship, meaning the effect becomes more pronounced over longer observation periods. For instance, the difference in BMD gain between 6 and 12 months is substantial. As the baseline level of vitamin D increases, the BMD gain decreases (coefficient = −0.253, $p < 0.0001$). For example, an increase in the baseline vitamin D level from 15 to 28 ng/mL results in a 4.8% reduction in gain. This confirms that patients with lower baseline vitamin D levels show greater increases. At levels ≥30 ng/mL, the total gain does not exceed 0.5%. The effect of age (coefficient = −0.051, $p < 0.0001$) suggests that each additional year of age reduces the gain by 0.051%. For instance, the difference in gain between patients aged 30 and 50 years is approximately 1.02%. A sex-based effect was also identified (coefficient = 0.388, $p = 0.039$), indicating that males had, on average, a 0.388% greater BMD gain.

When assessing BMD for the NNT group, a linear regression model demonstrated the best predictive performance: the adjusted R-squared was 0.8955, and the F-statistic was 206.7 ($p < 0.0001$). Coefficient analysis showed that with increasing observation time, BMD reduction becomes more pronounced (coefficient = −0.122, $p < 0.0001$). Patients with higher vitamin D levels exhibited less BMD loss (coefficient = 0.089, $p < 0.0001$). With advancing age, the degree of BMD reduction increased (coefficient = −0.081, $p < 0.0001$). Males experienced less BMD loss compared to females (coefficient = 0.515, $p < 0.0001$).

In the final stage of analysis, the frequency and nature of complications were assessed ***(Table 2)***. The data presented refer to the number of implants, including each pedicle screw or interbody implant, allowing for a more objective complication analysis.

Detailed analysis of the nature of complications across patient groups has led to the following conclusions.

In the group with initially normal 25-(OH)D_3 levels, no screw loosening was recorded at any follow-up point. Three patients exhibited interbody implant migration, but further investigation revealed gross violations of postoperative care guidelines, likely contributing to this occurrence (it should be noted that this group was characterized by younger age and, consequently, a more active lifestyle). The displacements recorded two months after surgery did not progress and did not require surgical correction.

In the SRD group, loosening of four G1-grade screws was recorded in two patients. During dynamic follow-up, the severity of these findings did not progress, and no surgical correction was needed. Three cases of interbody implant migration within the vertebral body were registered at the 6-month follow-up. In one case, the migration worsened to G2 severity by the 8-month control check. No further negative dynamics were observed thereafter, and surgical intervention was not required.

The NNT group exhibited the highest rate of complications. Six months after surgery, loosening of 13 screws and migration of 5 cages were noted, and two patients underwent revision surgeries. After another 6 months, the number of cage displacements increased to 6, and the number of loosened screws increased to 25. Six revision surgeries were performed.

Most of the mentioned complications had no clinical manifestations. For instance, displacement of a cage within the vertebral body was often asymptomatic and did not adversely affect the patient's condition. G1-grade screw loosening was typically a radiological finding that did not require clinical intervention. However, it should be taken into account that many surgeons do not recommend routine follow-up CT scans to their patients,

Table 2. Frequency and nature of postoperative complications associated with implant placement

Indicator	0–6 months			0–12 months		
	NNC	SRD	NNT	NNC	SRD	NNT
Screws						
G0	44	256	251	44	256	239
G1	–	4	10	–	4	14
G2	–	–	2	–	–	5
G3	–	–	1	–	–	4
G4	–	–	–	–	–	2
Cages						
G0	25	85	62	25	85	60
G1	2	3	3	2	2	3
G2	1	–	1	1	1	2
G3	–	–	1	–	–	1
Surgical correction	0	0	2	0	0	6

which may limit the detection of such complications. Therefore, our data may significantly exceed those of other studies on complications due to more rigorous radiological monitoring.

The conducted analysis allowed for the identification of certain findings scarcely covered in the literature. It was found that adequate correction of 25-(OH)D_3 levels can halt the process of screw loosening, thereby eliminating the need for revision surgeries. Insufficient levels of vitamin D_3 may result in interbody implant dislocation during the late postoperative period, which is traditionally considered uncharacteristic for the type of surgeries under discussion.

Statistical analysis supported the conclusion that correction of 25-(OH)D_3 levels using "Solemax®" significantly reduces the risk of postoperative complications. Within the first 6 months post-surgery, the risk of screw loosening decreased by 69.84% (odds ratio [OR] – 0.3016), and the risk of interbody implant migration – by 56.2% (OR – 0.438). After one year of follow-up, the risk reduction amounted to 85.06% (OR – 0.1494) for screw loosening and 64.7% (OR – 0.353) for PLIF implant migration. However, it is evident that such a reduction in risks cannot be attributed solely to the positive effect of 25-(OH)D_3 on BMD, as the changes in this parameter during the observed period were not sufficient to explain the magnitude of the effect. It is likely that the identified correlation is related to more complex mechanisms, some of which are discussed below.

Clinical Case

Patient S., 59 years old, underwent surgical intervention due to instability of the L5–S1 segment on the background of Spina bifida at S1. An interbody corporodesis was performed using a PEEK cage along with transpedicular fixation at the L5–S1 level. During screw placement, looseness of the bone tissue was noted. The BMD index of the L1 vertebral body was 85 HU. The level of 25-(OH)D_3 measured 10 days postoperatively was 18.7 nmol/L. The patient was advised to undergo an examination to rule out osteoporosis and, if necessary, initiate appropriate therapy.

Four months after surgery, a follow-up examination revealed early signs of screw instability graded G1 in the S1 vertebral body ***(Fig. 6B)***. The patient provided DEXA scan results indicating early signs of osteopenia and a conclusion from the endocrinologist stating that no specific therapy was required.

Eight months postoperatively, due to the onset of dull pain in the postoperative area, a control CT scan was performed ***(Fig. 6C)***, which revealed progression of screw instability to grade G2. At month 11, a revision surgery was carried out. The screws were replaced with larger-diameter screws impregnated with polymethylmethacrylate, and additional screws were placed in the iliac wings to reinforce the fixation.

Discussion

In assessing the effectiveness of using vitamin D_3 for the prevention of complications associated with implant placement, a brief overview of its biological effects and impact on the skeletal system is necessary for proper interpretation of the obtained results. It is known that approximately 80–90% of vitamin D_3 is synthesized in the skin under the influence of ultraviolet radiation, while 10–20% is obtained from food sources [30]. This ratio depends on a number of factors, including lifestyle, climate, geographical latitude, skin pigmentation, age, and dietary habits. For instance, in populations residing at higher latitudes (e.g., Scandinavian countries and Canada), cutaneous synthesis of vitamin D_3 decreases during the autumn and winter months, shifting the ratio toward dietary sources. It has been established that the peak intensity of synthesis occurs under direct sun exposure at midday, with an optimal wavelength range of 295–315 nm (UVB spectrum) [31].

The precursor of vitamin D in the skin is 7-dehydrocholesterol, a cholesterol derivative found primarily in the deeper layers of the epidermis. Ultraviolet exposure triggers a photochemical reaction resulting in the cleavage between the 9th and 10th carbon atoms in the ring structure of 7-dehydrocholesterol, forming an unstable compound, previtamin D_3. Within several hours, body heat induces thermal isomerization of this compound into a stable form – vitamin D_3

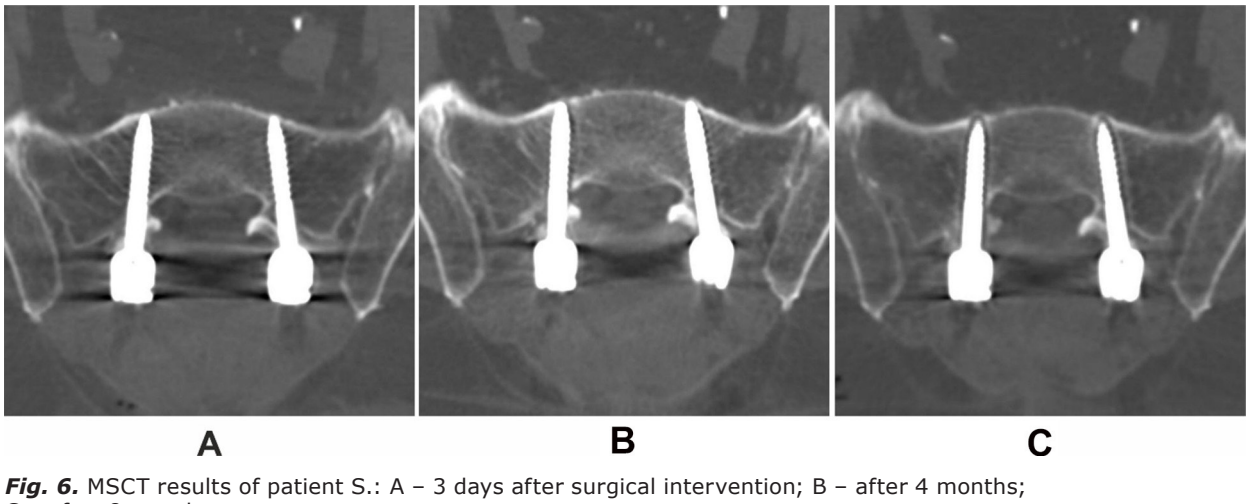

Fig. 6. MSCT results of patient S.: A – 3 days after surgical intervention; B – after 4 months; C – after 8 months.

(cholecalciferol). Several studies have shown that with excessive UVB exposure, previtamin D_3 can be converted into other metabolites such as toxisterol or lumisterol, which do not initially participate in calcium metabolism but possess antioxidant properties [32, 33]. This mechanism serves as a safeguard against excessive production of vitamin D_3 [34]. The greater the surface area of skin exposed to sunlight, the more vitamin D_3 is synthesized. Research indicates that even UVB exposure to as little as 5% of skin surface area (e.g., the face and hands) can significantly affect serum levels of 25(OH) D [35, 36]. Sunscreens with SPF ≥50 reduce vitamin D_3 synthesis by 75–90% [37]. Additionally, melanin in the skin absorbs ultraviolet radiation, thereby reducing its availability for vitamin D_3 synthesis. As a result, individuals with darker skin (Fitzpatrick skin types V and VI) exhibit a slower synthesis rate [38]. With aging, the level of 7-dehydrocholesterol in the epidermis decreases, leading to a reduced capacity for vitamin D_3 synthesis. Consequently, elderly individuals are more vulnerable to vitamin D deficiency, especially when sun exposure is limited [39].

The second route of cholecalciferol entry into the body is alimentary—primarily through the consumption of animal-derived foods. However, it has been noted that achieving adequate vitamin D intake through a standard diet is difficult. In several countries, this deficiency is compensated through the use of vitamin D-fortified foods or dietary supplements [40, 41]. Research by D.R. Fraser demonstrates that endogenously synthesized vitamin D_3 possesses higher biological activity compared to exogenously obtained vitamin D_3 [42].

Once in the bloodstream, vitamin D_3 almost immediately binds to transport proteins, which protects it from degradation and helps maintain its concentration in circulation. More than 85% of cholecalciferol is transported by vitamin D-binding protein (DBP), which exhibits a high affinity not only for vitamin D itself but also for its hydroxylated forms [43, 44]. Approximately 15% is transported by albumin; however, due to its lower binding specificity, this mode of transport facilitates faster cellular uptake of vitamin D [45]. Less than 1% of vitamin D_3 exists in its free form, which is considered biologically active and capable of entering cells to activate the expression of genes involved in calcium homeostasis, immune response, cell proliferation, and differentiation [46].

The liver is the primary organ involved in the initial stage of vitamin D_3 metabolism. Cholecalciferol, bound to DBP, is delivered to the liver via the portal vein or systemic circulation. The DBP–vitamin D_3 complex is recognized by specific receptors on the hepatocyte membrane, resulting in endocytosis that enables the intracellular entry of vitamin D_3. Within the cell, it undergoes hydroxylation catalyzed by the enzyme 25-hydroxylase (CYP2R1), producing 25-hydroxyvitamin D_3($25(OH)D_3$), which represents the main circulating form of the vitamin [47]. The resulting $25(OH)D_3$ binds to DBP and re-enters the bloodstream, from where it is transported to the kidneys for further activation or stored in depots, primarily adipose tissue [43]. The concentration of $25(OH)D_3$ is commonly used as a biomarker for assessing vitamin D status in the body, as it reflects the combined vitamin D_3 intake from both skin synthesis and dietary sources, although it possesses very low biological activity [44].

The next stage of metabolism involves the hydroxylation of the biologically less active calcidiol ($25(OH)D_3$) to form calcitriol ($1,25(OH)_2D_3$)—the active form of vitamin D_3, which performs key biological functions in the body within the context of the processes analyzed in this study. This transformation process occurs under the action of the enzyme 1α-hydroxylase (CYP27B1). Under conditions of relative homeostasis, approximately 85–90% of $1,25(OH)_2D_3$ is synthesized in the kidneys, while 10–15% is produced in other tissues, primarily bone, cartilage, and connective tissues. It has been established that bone structure restoration, such as after trauma, can significantly alter this ratio in favour of local transformation. Calcidiol is transported through the renal arterioles to the epithelium of the proximal convoluted tubules in the form of the DBP-$25(OH)D_3$ complex. Endocytosis occurs here via megalin and cubilin receptors, and hydroxylation at the 1α-position of $25(OH)D_3$ takes place intracellularly. CYP27B1, being the key enzyme in the activation of vitamin D_3, represents a crucial regulatory point in this process via mechanisms of both positive and negative feedback regulation [48]. Specifically, direct stimulation of CYP27B1 gene expression in proximal tubule cells of the kidneys is observed during hypophosphatemia and under the influence of parathyroid hormone (PTH). Elevated calcium levels can inhibit the activity of CYP27B1 either directly in the proximal tubule cells or indirectly by stimulating calcium-sensing receptors (CaSR) on parathyroid gland cells, leading to suppressed PTH secretion [49].

It is noted that calcitriol synthesized in the kidneys primarily exerts systemic effects. In the intestines, for example, $1,25(OH)_2D_3$ plays a key role in enhancing the absorption of calcium and phosphate. Calcitriol enters the epithelial cells of the small intestine (mainly the duodenum and jejunum) and binds to vitamin D receptors (VDRs) located in the cell nucleus. The calcitriol-VDR complex activates the expression of genes responsible for the synthesis of a number of transport proteins: Calbindin-D—a calcium-binding protein that transports calcium through the cytoplasm of enterocytes from the apical membrane to the basolateral membrane; TRPV6 (a calcium channel)—a channel located on the apical membrane of enterocytes through which calcium enters the cell from the intestinal lumen; PMCA1b (a calcium pump)—a protein on the basolateral membrane that actively transports calcium from the cell into the bloodstream; NaPi-IIb (a sodium-phosphate cotransporter), which transfers phosphates from the intestinal lumen into the cell along with sodium ions, etc. [50]. Moreover, $1,25(OH)_2D_3$ enhances the reabsorption of calcium and phosphate in the proximal tubules, thereby reducing their urinary excretion. It also regulates immune cell functions (including macrophages, T-lymphocytes, and dendritic cells) by modulating the inflammatory response, suppresses the synthesis of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), participates in the regulation of the renin–angiotensin–aldosterone system by inhibiting the expression of the renin gene in the juxtaglomerular cells of the kidneys, which leads

to decreased production of angiotensin II—a potent vasoconstrictor and a contributor to elevated blood pressure. Additionally, it improves endothelial function by increasing the synthesis of nitric oxide, which promotes vasodilation, inhibits vascular wall mineralization by reducing the expression of osteopontin and β-glycan and increasing the production of matrix Gla-protein (MGP), and improves myocardial contractility through modulation of intracellular calcium levels [51, 52].

In the context of the analyzed issue, significantly greater interest lies in the local synthesis of $1,25(OH)_2D_3$ within bone tissue, since renal calcitriol plays a leading role in supplying the bone with calcium and phosphate via systemic calcium-phosphorus homeostasis, whereas local $1,25(OH)_2D_3$ is crucial for the fine-tuned regulation of bone remodeling and regeneration processes. Upon entering from the bloodstream in the form of DBP-25(OH)D_3, calcidiol is converted into calcitriol in all major types of bone cells (osteoblasts, osteoclasts, and osteocytes) via the enzyme CYP27B1 [53]. The primary mechanism of intracellular transport of the DBP-25(OH)D_3 complex is mediated by megalin, which is predominantly expressed in osteocytes and osteoblasts of bone tissue. Several studies demonstrate a significant age-related decline in megalin expression, particularly in proximal tubular cells of the kidneys, which reduces substrate availability for $1,25(OH)_2D_3$ synthesis due to diminished reabsorption of DBP-25(OH)D_3 from the bloodstream [54]. A similar trend in bone tissue has not been definitively proven, although a general age-associated decline in the activity of osteoblasts and osteocytes has been verified, which may indirectly affect intracellular transport of DBP-25(OH)D_3. Furthermore, an age-related decrease in systemic CYP27B1 activity has been recorded, which is of fundamental significance for the development of osteoporosis. A number of experimental studies in animals demonstrate a nearly linear correlation between the age-related decline in CYP27B1 activity in bone tissue and the reduction in BMD [55,56].

Unlike the renal parenchyma, where CYP27B1 expression is regulated by systemic factors, in bone tissue, the primary stimuli for the expression of this enzyme are mechanical loading, bone tissue damage, and the inflammatory response [57]. These local stimuli activate CYP27B1, promoting the synthesis of calcitriol, which participates in the local regulation of bone metabolism and ensures a certain degree of autonomy in both adaptive and reparative processes [58].

It is well established that bone tissue is capable of dynamically responding to mechanical forces within physiological limits. In fact, the microarchitecture of bone is shaped by habitual mechanical loading, maintaining a balance between strength and mass economy [59]. The trabecular structure of the spongy substance of the vertrbra, according to Wolff's law, clearly reflects the vectors of compression and tension generated during axial and lateral loading [60]. The fundamental structural-functional element of bone tissue responsible for remodeling in response to mechanical load is the osteocyte—a cell located within lacunae in the mineralized matrix and interconnected through a canalicular system filled with interstitial fluid. Mechanical loading induces micro-deformations in the bone, causing interstitial fluid to flow through the canaliculi surrounding osteocyte processes. This results in the activation of mechanoreceptors and ion channels, triggering a cascade of intracellular signals. The main pathways involved are the Wnt/β-catenin signaling pathway, prostaglandins (PGE_2), and nitric oxide, which stimulate nearby osteoblasts and increase the expression of CYP27B1 [61, 62].

In response to mechanical injury to bone tissue, a complex process is initiated that involves an inflammatory reaction and remodeling aimed at restoring bone structure and function. The initial stage of this pathophysiological process is the production of pro-inflammatory mediators (IL-1β and TNF-α) by osteoblasts and macrophages, which in turn stimulate CYP27B1 expression in bone cells. The increased synthesis of calcitriol accelerates the remodeling of damaged bone by stimulating osteoblasts and the production of bone matrix, while the activation of osteoclasts via the RANKL/OPG system serves to remove damaged tissue [63, 64].

Calcitriol synthesized locally within bone tissue exerts a potent anti-inflammatory effect. Upon binding to the VDR, it suppresses the expression of genes encoding key pro-inflammatory cytokines (IL-1β, TNF-α, and IL-6), while simultaneously stimulating the production of anti-inflammatory cytokines (IL-10 and transforming growth factor-beta, TGF-β). Under its influence, macrophage polarization shifts from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype. Additionally, calcitriol inhibits the activation of Th17 cells, which produce IL-17—a cytokine associated with bone tissue destruction [65]. Calcitriol also plays an important role in the regulation of osteoclastogenesis: it decreases RANKL expression while enhancing the synthesis of osteoprotegerin (OPG), which binds to RANKL and prevents its interaction with the RANK receptor, thereby limiting osteoclast activity [66]. This mechanism allows for a balanced inflammatory response at the initial stage, enabling the osteolysis of damaged structures while preventing excessive bone degradation and the transition to a chronic inflammatory state. Thus, calcitriol counteracts the hyperactivation of osteoclasts characteristic of chronic inflammation and contributes to the preservation of bone mass by maintaining the balance between bone resorption and regeneration [67]. This mechanism is particularly critical for preventing the destructive consequences of prolonged inflammatory processes.

The simplified mechanism of vitamin D biological activity in bone tissue described above—both under physiological conditions and in the presence of pathology—provides a rationale for a pathogenetic approach to correcting its deficiency during surgical spinal stabilization using implants. From a pathophysiological standpoint, the process of implantation involves bone tissue damage, an inflammatory response, and load redistribution. This process can be illustrated using the example of transpedicular stabilization. The placement of transpedicular screws results in mechanical destruction of trabecular and, to a lesser extent, cortical bone, which induces a local tissue response (activation of osteoclasts, osteoblasts, and immune cells, initiating bone remodeling). In response to injury,

proinflammatory mediators (IL-1β, TNF-α, IL-6) are released, which stimulate osteoclastogenesis and recruit macrophages and other immune cells. The inflammatory response plays a dual role: on the one hand, it prepares the contact area for subsequent healing and osseointegration; on the other hand, excessive activation may lead to increased bone resorption and decreased screw stability [68]. Furthermore, the installation of transpedicular screws alters the biomechanical environment of the spine: the screws absorb part of the load, redistributing it between the bone and the implant [69]. This necessitates an adaptive response of the bone tissue surrounding the screws, manifested in enhanced activation of osteoblasts to form new bone tissue and ensure construct stability [70].

In the context of the issue under analysis, and based on current research devoted to the pathophysiology of bone tissue, it can be concluded that the stability of spinal fusion is determined more by the adequacy of bone tissue response to implantation than by absolute BMD values. Thus, even in cases of low BMD, successful osseointegration and adaptive remodeling can provide sufficient stability, provided there is an adequate distribution of load; conversely, when bone mineral density is normal but the tissue response to implantation is insufficient, the risk of construct instability remains high. This conclusion is supported both by the results of our study and by findings from other authors, though it requires further comprehensive investigation due to its clinical significance [71, 72].

Overall, the data we obtained demonstrate the advisability of correcting vitamin D levels in patients who have undergone spinal surgery involving the installation of various types of implants (including transpedicular fixation systems and cages for interbody fusion). This is supported by data from a limited number of studies. For example, Yong Xu et al. conducted an analysis of the efficacy of using $1,25(OH)_2D_3$ following TLIF (transforaminal lumbar interbody fusion) [73]. The authors noted that six months after surgery, the interbody fusion rate was 76.19% in the treatment group versus 43.48% in the comparison group ($p = 0.03$). Further follow-up revealed rates of 95.24% and 65.22%, respectively ($p = 0.02$). Moreover, in patients receiving $1,25(OH)_2D_3$, the Oswestry Disability Index (ODI) scores at all stages of follow-up were statistically significantly lower than in the comparison group.

V.M. Ravindra et al. reported results from a prospective observational study examining the frequency and rate of fusion and stability of spinal fusion in patients who underwent elective surgery using transpedicular screws [74]. Comparing patient groups with vitamin D deficiency (<20 ng/mL), insufficiency (20–30 ng/mL), and normal levels (>30 ng/mL), a significant increase in the median time to achieve fusion was observed (12, 8, and 6 months, respectively; $p = 0.001$). Furthermore, a multivariate analysis considering age, sex, and fusion length showed that vitamin D deficiency is an independent factor associated with failure to achieve adequate bony fusion. Similar results were obtained by other researchers [75, 76].

A review of the existing literature reveals that a number of studies are dedicated to the impact of baseline vitamin D levels and their correction on the overall efficacy of elective spinal surgery, which affects quality of life and is assessed using specialized questionnaires. Thus, Hao-Wei Xu et al., based on an evaluation of outcomes in 360 patients who underwent PLIF or TLIF procedures combined with transpedicular screws, determined that preoperative $25(OH)D_3$ deficiency is associated with poorer outcomes on the Visual Analogue Scale (VAS), the Japanese Orthopaedic Association (JOA) questionnaire, and ODI in the early postoperative period [77]. Similar findings were reported by Tae-Hwan Kim et al. [78]. These researchers analyzed outcomes in 31 female patients who underwent decompressive-stabilizing surgery on the lumbar spine for spinal canal stenosis. Treatment outcomes were assessed using the EuroQol-5D quality of life questionnaire and ODI. It was established that, in the postoperative period, correction of $25(OH)D_3$ levels was statistically significantly correlated with the patients' subjective evaluations of the surgical outcomes.

This phenomenon pertains to another aspect of vitamin D influence that is not addressed in this study. It is well-established that the stability of the spinal motion segment, both under normal conditions and post-surgery, is determined not only by the condition of the bone structures but also, to a significant extent, by the state of the ligamentous apparatus [79]. The degree of influence of the latter is inversely proportional to the rigidity of the applied fixation, yet it almost always contributes to the provision of stability [80]. The primary component that determines the mechanical properties of the human spinal ligamentous apparatus are type I and III collagens (COL1 and COL3) and elastin (ELN), whose concentrations vary across different ligaments. Thus, in the posterior ligamentous complex, which has the most significant impact on spinal motion segment stability, the ratio of COL1, COL3, and ELN is as follows: in the supraspinous ligament – 90–95%, 5–10%, and <5% respectively; in the interspinous ligament – 70–80%, 20–30%, and 5–10%; in the ligamentum flavum – 20–30%, 5–10%, and 60–70%; and in the posterior longitudinal ligament – 80–85%, 10–15%, and 5% [81].

A number of studies have demonstrated that in cases of ligamentous apparatus injury, which is inevitable during surgical intervention, vitamin D levels often become a critical factor influencing the speed and quality of regeneration [82]. Vitamin D activates VDRs in fibroblasts, enhancing their proliferative activity and increasing the expression of genes encoding COL1, COL3, and ELN. This contributes to the restoration of the structure of damaged ligaments, inhibits collagenase activity—thereby preserving ligament integrity and preventing degradation—and stimulates angiogenesis through the production of vascular endothelial growth factor (VEGF), ensuring oxygen and nutrient delivery to damaged tissues and accelerating healing. Furthermore, vitamin D regulates the activity of matrix metalloproteinases and their inhibitors, thereby enabling balanced degradation of the damaged matrix and synthesis of new matrix components. It promotes the differentiation of mesenchymal stem cells into fibroblast-like cells, increasing their role in regeneration, and modulates immune responses, protecting the injury site from secondary infection and creating a favorable environment for healing [83]. These mechanisms have

a significant indirect impact on the effectiveness of spinal fusion and on the overall outcome of surgical intervention.

One of the most effective strategies for enhancing the effects of vitamin D on bone tissue, according to contemporary research, is its combined use with vitamin K_2 [84,85]. Vitamin K_2 (menaquinone, MK) is a fat-soluble vitamin that plays a crucial role in calcium metabolism, as well as in maintaining the normal metabolism of bone tissue and cardiovascular health. The main sources of menaquinones include fermented foods (e.g., natto, cheese, sauerkraut) and animal products (e.g., egg yolk, liver, fatty fish). Vitamin K_2 exists in several forms, among which MK-4 and MK-7 are the most significant, differing in metabolic activity and bioavailability. MK-4 is the only form of menaquinone synthesized in the human body. The substarate for synthesis is phylloquinone vitamin K1, which is obtained from dietary sources, primarily green leafy vegetables (spinach, broccoli, cabbage) and plant oils. The key enzymes involved in the conversion of K1 to MK-4 are NAD(P)H reductase and isoprenoid transferase, and this process occurs directly within the tissues where MK-4 performs essential biological functions. A distinctive feature of MK-4 is its high bioavailability and short half-life; its tissue levels depend on the presence of vitamin K1 in the diet. In contrast, MK-7, which is obtained solely through dietary intake, has a long side chain composed of seven isoprenoid units. This structure ensures high stability and a half-life of approximately 72 hours, making it particularly effective when consumed regularly in low doses, as it accumulates in the body [86].

The primary mechanism by which vitamin MK influences bone tissue metabolism—justifying its use alongside vitamin D3—lies in the activation of osteocalcin, a protein involved in bone mineralization. Osteocalcin is synthesized by osteoblasts in an inactive form, and MK plays a key role in its activation by serving as a cofactor for the enzyme γ-glutamyl carboxylase. This enzyme catalyzes the addition of γ-carboxyl groups to glutamic acid residues. The activated form of osteocalcin exhibits high affinity for calcium and hydroxyapatite crystals ($Ca_{10}(PO_4)_6(OH)_2$), the main mineral component of bone tissue. Upon binding to these components, osteocalcin is integrated into the mineral matrix, fulfilling a stabilizing function and ensuring the structural integrity of the bone. This process promotes effective mineralization of bone tissue and supports its mechanical strength [87].

In addition, MK reduces the risk of vascular calcification, preserving vascular elasticity and preventing the development of atherosclerosis. A key player in preventing calcium salt deposition in soft tissues is matrix Gla-protein (MGP)—a protein primarily synthesized by vascular smooth muscle cells, chondrocytes, and bone cells. Its expression is regulated by vitamin D through binding to the vitamin D receptor VDR, which enhances gene transcription and increases MGP mRNA synthesis. MGP activation occurs in the endoplasmic reticulum via γ-glutamyl carboxylase, which also uses vitamin K_2 as a cofactor. Following γ-carboxylation, activated MGP is transported from the cell into the extracellular matrix, where it binds calcium ions, preventing their precipitation and the formation of hydroxyapatite crystals in soft tissues [88]. Calcium ions bound by activated MGP are returned to the bloodstream through the action of specific cellular transport systems. Voltage-gated calcium channels (VGCC) facilitate the passive influx of calcium into cells along the concentration gradient, while Plasma Membrane Ca^{2+}-ATPase (PMCA) actively exports calcium from endothelial cells into the bloodstream. This process maintains calcium homeostasis, prevents pathological vascular calcification, and preserves vascular functionality by ensuring arterial wall elasticity and reducing the risk of atherosclerosis [89].

Thus, beyond the evident synergism in maintaining normal bone metabolism, the combined use of vitamin D3 and MK is significantly safer—particularly in preventing pathological calcification of soft tissues and ensuring optimal calcium distribution in the body. The administration of D3 without K2 carries the risk of elevated free calcium levels that cannot be effectively redirected into bone tissue. In contrast, their co-administration creates a balanced calcium regulation system, thereby minimizing associated risks [90].

The aforementioned data obtained from *in vitro* studies have been confirmed in clinical practice. For instance, Jun Iwamoto et al. conducted an evaluation of the effects of combined administration of vitamins D_3 and K_2 on BMD of the lumbar spine in postmenopausal women with verified osteoporosis [91]. The study included 92 postmenopausal women diagnosed with osteoporosis who had been in menopause for over five years and were aged between 55 and 81 years. The participants were randomized into four treatment groups: the first group received vitamin D_3, the second — vitamin K_2, the third — a combination of vitamins D_3 and K_2, and the fourth — calcium lactate. It was found that intake of either vitamin D_3 or vitamin K_2 over a period of two years significantly increased BMD of the lumbar spine, whereas calcium intake led to a significant decrease in this parameter. Combined administration of vitamins D_3 and K_2 resulted in a marked increase in lumbar spine BMD, more pronounced than in monotherapy with either vitamin D_3 or K_2. A similarly designed study was conducted by Takahisa Ushiroyama et.al [92]. A total of 172 women aged 55–81 years, who had signs of osteoporosis or osteopenia according to BMD measurements, were divided into four statistically equivalent groups. These groups received vitamin K_2, vitamin D_3, combined therapy with vitamins K_2 and D_3, or dietary support alone. The latter group was provided with recommendations to increase intake of foods rich in vitamins D_3 and K_2, consume 800–1000 mg of calcium daily (primarily from dairy products such as milk and yogurt), take mineral supplements, engage in moderate physical exercise, and spend at least 15 minutes per day in direct sunlight. A significant increase in BMD was observed in 45.2% of patients in the combined therapy group, in 9.4% of the K_2 group, and in 23.3% of the D_3 group. Participants in the comparison group did not show significant improvement in BMD, and in some cases, a decline in the assessed parameter was noted. Similar findings are reported by other researchers [93–95].

We have considered only a small portion of the biological effects that demonstrate the clinical significance of correcting vitamin D_3 levels in patients who have undergone spinal surgery involving implants. The impact of vitamin D_3 on the incidence of inflammatory

complications, pain intensity, rehabilitation rate, and other aspects was not studied in this research. However, these issues require further investigation, as they significantly influence patients' quality of life and clinical outcomes. Further exploration of these aspects may broaden our understanding of the role of vitamin D_3 in the postoperative period and contribute to optimizing treatment strategies for such patients.

Conclusions

A high frequency of vitamin D deficiency and decreased BMD was recorded among patients undergoing elective spinal surgeries involving implants. A significant correlation was found between the level of 25-(OH)D_3 and bone tissue status.

Correction of vitamin D_3 levels using "Solemax®" demonstrated a pronounced laboratory effect: after four months of intake, the 25-(OH)D_3 level in all patients reached the reference values, indicating the efficacy of this therapy.

Regular "Solemax®" intake in the postoperative period had a positive effect on bone tissue condition. This was confirmed by an increase in BMD among patients receiving correction therapy, while a decrease in this parameter was registered in the comparison group.

A statistically significant reduction in the incidence of implant-related complications was observed in patients who received "Solemax®" starting from the early postoperative period. Regular intake reduced the risk of screw loosening by 69.84% and the risk of interbody implant displacement by 56.2% within the first 6 months post-surgery. After 1 year of follow-up, the risk reduction was 85.06% for screw loosening and 64.7% for PLIF implants.

The obtained results indicate that the stability of spinal fusion is determined primarily by the qualitative adaptive response of bone tissue to implantation rather than the absolute values of its mineral density. The use of a balanced combination of vitamins D_3 and K_2 significantly enhances the therapeutic effect, reduces the risk of postoperative complications, and improves clinical outcomes.

Disclosure

Conflict of interest

The company provided the investigational drug as a trial batch. No financial support was received from the company. The study design was developed by the authors. Data analysis and formulation of conclusions were conducted solely by the authors. The authors declare no conflicts of interest.

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