

Original Communication

# Impact of High Doses of Vitamin D on Specific Metabolic Parameters in Type 2 Diabetes Patients: A Prospective Biomedical Study

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## Abstract

**Background/Objectives:** Vitamin D is a pleiotropic molecule involved in various physiological processes beyond skeletal health, including immune modulation and metabolic regulation. This prospective observational biomedical study aimed to assess the impact of short-term high-dose vitamin D supplementation on selected metabolic parameters in adult patients with type 2 diabetes mellitus (T2DM) and low serum 25-hydroxyvitamin D [25(OH)D] concentrations. **Methods:** Thirty patients were enrolled and assigned to receive either 10,000 IU/day of cholecalciferol (Group A) or a significantly lower dose (960 IU/day, Group B) for 12 weeks based on recruitment order (odd/even identification numbers). The primary endpoints were changes in parathyroid hormone (PTH), fasting blood glucose (FBG), calcium, phosphorus, and glycated haemoglobin (HbA1c). **Results:** A strong, statistically significant negative correlation between changes in 25(OH)D and PTH (Spearman  $r = -0.69052$ ,  $p = 0.0044$ ) was also observed. In the high-dose group, 25(OH)D increased from 17.2 to 31.8 ng/mL (median change 13.3 ng/mL), while PTH decreased from 3.27 to 2.76 pmol/L (median change  $-0.27$  pmol/L). In the lower-dose group, 25(OH)D increased from 18.5 to 28.2 ng/mL (median change +8.1 ng/mL). The increase in 25(OH)D was significantly greater in the high-dose group than in the lower-dose group (median change +13.3 vs +8.1 ng/mL,  $p = 0.015$ ). Within the observed range, patients with larger increases in 25(OH)D tended to show greater reductions in PTH. Other metabolic markers (HbA1c, FBG, calcium, and phosphorus) remained stable over 12 weeks. **Conclusions:** These findings support the effectiveness and safety of high-dose vitamin D supplementation in correcting vitamin D deficiency and reducing PTH levels in patients with T2DM while highlighting the need for longer-term studies to evaluate its broader metabolic effects.

**Keywords:** vitamin D; cholecalciferol; high-dose supplementation; type 2 diabetes mellitus; 25-hydroxyvitamin D; parathyroid hormone; HbA1c; fasting blood glucose

## 1. Introduction

Vitamin D is believed to be one of the earliest hormones produced in evolutionary history, dating back to the emergence of eukaryotic organisms in the oceans more than 1.5 billion years ago. Supporting evidence comes from the observation of the phytoplankton species *Emiliana huxleyi*, which has existed in its current form in the Sargasso Sea for more than 750 million years. This organism contains ergosterol (provitamin D<sub>2</sub>; approximately 1 µg/g dry weight), which can be photoconverted into previtamin D<sub>2</sub> upon exposure to simulated sunlight [1]. Since the chemical structure of vitamin D was first elucidated in 1930—an achievement for which Adolf Otto Reinhold Windaus was awarded the Nobel Prize—research on this molecule has expanded substantially [2]. The number of publications on vitamin D has increased dramatically, with PubMed showing a progression from a single article in 1922 to 110 in 1952, 740 in 1982, and 5566 in 2020. This surge reflects a growing understanding that vitamin D plays a far broader biological

role than initially thought. Early studies focused primarily on its effects on calcium homeostasis and bone metabolism [3].

The discovery of 25-hydroxyvitamin D [25(OH)D] in 1968 and the subsequent identification of the active form, 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D], opened new lines of investigation into its roles in immunity, infectious diseases, cancer, and cardiovascular health [4]. Beyond skeletal effects, vitamin D is now recognized as a key immunomodulator, influencing phosphate absorption in the gut and reducing renal excretion. Although its role in bone health is well established, this represents only one of many functions. Vitamin D is considered a pleiotropic molecule, meaning it exerts influence over multiple biological systems simultaneously. Pleiotropy refers to the phenomenon in which a single gene or compound affects multiple phenotypic traits [5]. Beyond its classical role in calcium-phosphate homeostasis, vitamin D acts as a pleiotropic hormone with wide-ranging extraskelatal actions. Several tis-



sues not primarily involved in mineral metabolism express the vitamin D receptor (VDR), and some also express  $1\alpha$ -hydroxylase, enabling local conversion of 25(OH)D to its active form and supporting autocrine and paracrine signalling. Through these pathways, vitamin D modulates cell proliferation and differentiation, hormone secretion, vascular and cardiac function, and both innate and adaptive immune responses. Clinical and experimental evidence therefore links vitamin D status not only to bone health but also to a broad spectrum of chronic, inflammation-related conditions, including cardiovascular disease, inflammatory bowel disease, and age-related functional decline, although results from large intervention trials remain heterogeneous [6–8]. Today, vitamin D is among the most widely used substances in both medicine and pharmacy. Dietary intake is often insufficient because only a limited number of foods naturally provide adequate amounts. Thus, cutaneous synthesis triggered by sunlight exposure remains the primary source. It was long assumed that vitamin D status was passively regulated. However, nearly a century after its discovery, it is now understood that vitamin D is biologically inactive in its native form, requiring complex enzymatic activation and functioning with hormone-like properties, similar to those of steroid hormones [9].

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder closely associated with low-grade chronic inflammation. This inflammatory state is characterized by elevated levels of acute-phase proteins and multiple inflammatory mediators, which play a crucial role in the development of insulin resistance and pancreatic  $\beta$ -cell dysfunction [10]. Beyond these direct metabolic effects, vitamin D has also been implicated in the low-grade inflammatory milieu characteristic of type 2 diabetes. In newly diagnosed T2DM, low 25(OH)D concentrations are almost universal and correlate with higher levels of interleukin-6, tumor necrosis factor- $\alpha$ , high-sensitivity C-reactive protein, malondialdehyde, and fibroblast growth factor-21, whereas vitamin D shows a positive association with adiponectin. These findings suggest that vitamin D deficiency may contribute to metabolic dysregulation by promoting a pro-inflammatory and pro-oxidative state and by unfavourably altering adipokine profiles in the early stages of T2DM [11,12].

Observational evidence further links low vitamin D status to inflammation-driven complications of type 2 diabetes. In patients with T2DM, those with coexisting non-alcoholic fatty liver disease (NAFLD) have significantly lower 25(OH)D levels and a markedly higher prevalence of vitamin D deficiency, which emerges as an independent risk factor for NAFLD in multivariable analyses. Similarly, in diabetic nephropathy, vitamin D deficiency clusters with elevated TNF- $\alpha$  (tumor necrosis factor- $\alpha$ ), IL-6 (interleukin-6), C-reactive protein, and chemerin, and these inflammatory mediators, together with low 25(OH)D levels, are among the strongest predictors of albuminuria in

type 2 diabetes. The association between low 25(OH)D levels and systemic inflammation is not restricted to diabetes [13,14].

In the geriatric population, a large systematic review and meta-analysis showed that individuals with higher inflammatory marker levels have significantly lower vitamin D concentrations, and vitamin D deficiency is consistently linked to a wide range of chronic, inflammation-based conditions, including type 2 diabetes and cardiovascular disease. Furthermore, level 1 evidence from a meta-analysis in patients with T2DM indicates that vitamin D supplementation can reduce circulating inflammatory markers, even though randomized trials focusing on glycaemic outcomes alone have generally reported small or neutral effects on HbA1c and insulin resistance. Collectively, these findings support the concept that correcting vitamin D deficiency may attenuate chronic low-grade inflammation and related cardiometabolic complications in T2DM, while its influence on short-term glycaemic indices remains uncertain [15].

Through its receptor (VDR), vitamin D directly regulates the expression of genes critical to insulin secretion and insulin action pathways. Acting as an anti-inflammatory hormone, vitamin D modulates immune cells within metabolic tissues, reducing both local and systemic inflammation and thereby helping to prevent dysfunction of pancreatic islets, liver, and skeletal muscle [16]. It also contributes to immune regulation through effects on innate and adaptive immunity, inhibiting the production of pro-inflammatory cytokines and mitigating chronic low-grade inflammation, a key driver of insulin resistance [17]. Experimental and clinical evidence support a direct role of vitamin D in several steps of glucose homeostasis. Pancreatic  $\beta$ -cells express the VDR, and mice lacking a functional VDR exhibit impaired insulin secretion in response to a glucose load, whereas  $\beta$ -cell-specific VDR overexpression preserves  $\beta$ -cell mass and reduces islet inflammation. Vitamin D regulates insulin secretion through both genomic and non-genomic mechanisms: it increases transcription of the insulin gene and other genes involved in cytoskeletal organization and  $\beta$ -cell growth and rapidly modulates calcium flux and membrane depolarization in  $\beta$ -cells, facilitating exocytosis of insulin granules. In rodent models, short-term administration of  $1,25(\text{OH})_2\text{D}$  prevents dexamethasone-induced insulin resistance and acutely stimulates calcium influx and insulin release from isolated pancreatic islets, further supporting direct  $\beta$ -cell effects of active vitamin D metabolites [18,19].

Beyond the pancreatic islet, vitamin D may also influence insulin sensitivity in classical insulin target tissues. VDR and the activating enzyme CYP27B1 are expressed in skeletal muscle and other peripheral tissues, where vitamin D upregulates insulin receptor expression and may enhance insulin signalling, partly through activation of peroxisome proliferator-activated receptor- $\delta$  and modulation of oxida-

tive stress and glutathione homeostasis. Low 25(OH)D concentrations have been consistently associated with insulin resistance and related disorders such as obesity, type 2 diabetes, metabolic syndrome, non-alcoholic fatty liver disease, and polycystic ovary syndrome. Meta-analyses of randomized trials in patients with type 2 diabetes and NAFLD suggest that vitamin D supplementation can modestly improve FBG, fasting insulin, and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), although effect sizes are small and heterogeneous, and large trials in prediabetes have not demonstrated consistent improvements in  $\beta$ -cell function except in subgroups with severe baseline deficiency [20–22].

## 2. Methods

The aim of this study was to monitor the impact of cholecalciferol administration on serum vitamin D levels and selected clinical parameters in two groups of patients. The dietary supplements used were a sublingual spray delivering 10,000 IU/day (DeVit® Direct, Emergopharm, Poland) or drops providing 960 IU/day (DeVit®, Emergopharm, Poland), administered to adult patients aged 18 to 65 years attending an internal medicine outpatient clinic, diagnosed with type 2 diabetes mellitus and low vitamin D levels (<30 ng/mL), over a period of 12 weeks.

### 2.1 Study Design

This biomedical observational study is designed as an open-label, non-blinded, monocentric, and non-placebo-controlled investigation. It aims to assess the effects of cholecalciferol supplementation administered in an unconventional short-term high-dose regimen, with subsequent evaluation of diabetic and endocrine blood parameters. In addition, the study examines the safety profile of the administered dosing and patient satisfaction with the supportive therapy. Participants were allocated using an alternating (quasi-random) assignment based on recruitment order (odd/even identification numbers). The study is conducted in compliance with the following guidelines:

- Declaration of Helsinki of the World Medical Association—Ethical Principles for Medical Research Involving Human Subjects.
- Good Clinical Practice (GCP).
- TREND Statement recommendations for the design and reporting of non-randomized/quasi-experimental studies [23].

### 2.2 Population

Adult patients were enrolled based on predefined inclusion and exclusion criteria.

Inclusion criteria:

1. Signed informed consent and completion of patient education.
2. Adult patients of both sexes aged 18 to 65 years.

3. Diagnosed with type 2 diabetes mellitus and low serum vitamin D levels (<30 ng/mL).
4. Permitted treatment consisting of indicated therapies for the specified diagnoses, which must be recorded in the questionnaire.

Exclusion criteria:

- Use of medications containing cholecalciferol prescribed by a specialist physician.
- Significant gastrointestinal, renal, hepatic, pulmonary, endocrine, oncological, or cardiovascular disease.
- Clinical condition requiring a change in therapy.
- Presence of a mental disorder affecting memory (e.g., Alzheimer's disease).
- Any other reason at the discretion of the investigator that would render the participant unsuitable for enrolment.
- The physician may discontinue a participant's involvement at any time if deemed necessary for the participant's health or due to insufficient cooperation.
- The participant may withdraw from the biomedical research at any time without providing a reason and retains the right to continue treatment with the same physician.
- Participation in another clinical study.

### 2.3 Methodology

At the initial outpatient visit, a blood sample was collected to measure serum vitamin D levels. Upon meeting the inclusion criteria and being enrolled, each patient was assigned an identification number three days after the initial visit and was required to complete a questionnaire.

Group allocation was performed using an alternating assignment based on the order of recruitment. Consecutively enrolled participants received an incremental identification number; odd-numbered participants were allocated to Group A and even-numbered participants to Group B. Allocation was not based on smoking status or any other baseline characteristic.

Following enrolment, patients received a dietary supplement containing cholecalciferol for a 12-week period. After 4, 8, and 12 weeks of supplementation, patients attended follow-up visits during which blood samples were collected and analysed for the following parameters:

- a. HbA1c (glycated haemoglobin).
- b. PTH (parathyroid hormone).
- c. Ionized calcium.
- d. FBG (fasting blood glucose).
- e. Phosphorus.
- f. Vitamin D.

### 2.4 Intervention

For vitamin D supplementation, a dietary supplement containing 10,000 IU of cholecalciferol per dose was used. The product is a spray designed for sublingual administration. Each dose delivers 250  $\mu$ g of cholecalciferol suspended in medium-chain triglyceride (MCT) oil, with a to-

tal of 60 doses per container. The supplement is equipped with a certified Swiss-made dispenser, ensuring precise and uniform dosing. The distributor promotes the product as ideal for rapidly increasing serum vitamin D levels. Owing to its formulation, it is particularly suitable for individuals with malnutrition or swallowing difficulties, as absorption begins directly in the oral cavity.

The supplements used in this study are considered safe and have been widely utilized in households and outpatient clinics across Slovakia for several years. The primary reason for their selection was the anticipated advantage of the pharmaceutical form, dosing precision, and active ingredient content, which, in the intervention group, was expected to safely and effectively raise serum vitamin D levels within a short period. Participants in Group A received cholecalciferol 10,000 IU/day for 12 weeks. The group that did not receive the 10,000 IU cholecalciferol formulation was administered the dietary supplement at a dosage of two doses corresponding to a total of 960 IU of vitamin D. To avoid discouraging patients from supplementing their vitamin D intake, we selected a significantly lower dose compared with the intervention group, yet one that remains consistent with World Health Organization (WHO) recommendations for the general population.

### 2.5 Data Collection

Data were initially recorded in the patient's folder and entered into the patient logbook in written form. During the evaluation phase, the data were transferred into an electronic database used exclusively for the statistical analysis of the biomedical study. All data collected were kept confidential, with access restricted to authorized personnel (the principal investigator, study coordinator, and pharmacist). Data completion and validation were performed using available information sources. Each enrolled patient was registered in the participant identification sheet and assigned a specific number as the patient's identifier. This number replaced the patient's name and surname to ensure protection of personal data. The data collected and assessed by the pharmacist included demographic and social information, details on the patient's current health status, and their understanding of their therapy.

### 2.6 Statistical Analysis

Descriptive statistical methods were used to analyse the basic characteristics of the patients. Questionnaires were evaluated using descriptive statistical methods, and, in cases involving standardized questionnaires, official scoring calculators were applied first. Changes in metabolic parameters and their relationship with vitamin D levels were assessed. Non-parametric tests were used due to their robustness in the presence of non-normally distributed data. Data visualization was performed using box plots and scatter plots. Group comparisons were conducted using the Wilcoxon rank-sum test, Wilcoxon signed-rank test, and

Mann-Whitney U test. Correlation analysis was performed using Spearman's rank correlation coefficient.

### 2.7 Ethical Principles

Each participant provided written informed consent in accordance with local requirements after receiving a full explanation of the nature of the study. The informed consent form was signed before initiating any study-related procedures. The reviewing ethics committee approved the version of the consent form and ensured that it was written in a language that the participant could read and understand. The informed consent process complied with the principles outlined in the Declaration of Helsinki, current ICH guidelines, Good Clinical Practice (GCP), and applicable regulatory requirements.

The biomedical study entitled "Identification of Vitamin D Levels Following Short-Term High-Dose Supplementation in Diabetic Patients" was approved by the Ethics Committee of University Hospital Bratislava – Ružinov Hospital. The committee issued a favourable opinion on the proposed study protocol, reference number EK/041/2022, dated March 23, 2022, stating that the submitted documentation meets the committee's requirements and complies with applicable legislation.

## 3. Results

A total of 30 patients were enrolled. Of these, 9 patients completed only the baseline blood sampling and did not continue follow-up. Among the remaining participants, 16 were scheduled for follow-up assessments according to the protocol (Table 1). This subgroup consisted of 14 men and 2 women. The average age of the men was 57.4 years, while the average age of the women was 60.5 years. The average body mass index (BMI) in men was 31.3, indicating mild obesity, whereas the average BMI in women was 35.1. However, the female subgroup included only two participants: one with a BMI of 19.5, which is at the lower limit of the normal range, and the other with a BMI of 50.7, indicating severe morbid obesity. However, one participant did not attend the follow-up visit and therefore follow-up laboratory values were unavailable. Consequently, 15 participants with complete baseline–follow-up paired laboratory measurements were included in the final paired analyses.

A total of 62.5% of participants reported engaging in less than one hour of physical activity per day, 18.75% reported 1–2 hours daily, and another 18.75% reported more than 2 hours of daily physical activity. Only 6.25% reported spending at least 15 minutes per day in direct sunlight on 11 or more days per month; 31.25% reported 1–5 days per month; and 62.5% reported no such sunlight exposure during the past month. Additionally, 18.75% reported vitamin D supplementation within the past month at a dose of 1000–2000 IU per day. The same proportion (18.75%) reported being smokers. With regard to study groups, the intervention group (Group A) included 7 patients, compris-

**Table 1. Population enrolled in the study.**

Patient	Group	Age	Sex	Smoking	Height (m)	Weight (kg)	BMI	Hours of physical activity per day
12	B	66	M	No	1.83	86	25.7	Less than hour
4	A	46	M	No	1.84	112	33.1	Less than hour
13	B	58	M	No	1.85	140	40.9	More than 2 hours
2	A	46	M	No	1.76	105	33.9	1–2 hours
5	A	58	F	Yes	1.46	108	50.7	More than 2 hours
11	B	56	M	No	1.64	88	32.7	Less than hour
16	B	61	M	No	1.80	73	22.5	Less than hour
6	A	47	M	Yes	1.73	95	31.7	Less than hour
7	A	68	M	No	1.70	65	22.5	Less than hour
14	B	68	M	No	1.86	139	40.2	Less than hour
9	B	59	M	No	1.82	83	25.1	Less than hour
3	A	54	M	Yes	1.84	100	29.5	Less than hour
18	B	48	M	No	1.75	110	35.9	1–2 hours
8	A	63	F	No	1.52	45	19.5	More than 2 hours
21	B	74	M	No	1.84	83	24.5	1–2 hours
20	B	61	M	No	1.72	120	40.6	Less than hour

BMI, Body Mass Index; M, Male; F, Female.

ing 2 women and 5 men, with a mean age of 54.6 years. All smokers were in this group. The average BMI in this group was 31.6. The control group (Group B) included 9 patients, all male, with a mean age of 61.2 years and no smokers. The average BMI in this group was 32.0.

### 3.1 Statistical Analysis of Results

The aim of the analysis was to evaluate changes in selected metabolic parameters (PTH, HbA1c, calcium, glucose, and phosphorus) over the course of the study, both within individual patients and between groups receiving different doses of vitamin D. Correlations between these metabolic variables and vitamin D levels were assessed using correlation analysis. Changes in individual parameters over time were evaluated using paired tests. Group comparisons were performed to detect potential differences in the effectiveness of vitamin D dosing. Data were visualized using box plots to illustrate distribution and summary statistics at baseline and final visits and scatter plots to show correlations between variables. Choosing appropriate statistical tests was essential for obtaining reliable results. Because most variables did not follow a normal distribution (confirmed via the Shapiro–Wilk test), non-parametric tests were used. These methods are more robust for small sample sizes and outlier-prone data because they rely on ranks or medians rather than raw values. To verify baseline comparability between the groups, the Wilcoxon rank-sum test—a non-parametric alternative to the independent *t*-test—was used. A *p*-value greater than 0.05 was considered evidence that the groups were comparable at baseline. This step ensured that any later differences could be attributed to the intervention rather than to pre-existing disparities. The Wilcoxon signed-rank test was used to compare repeated measures within the same patients (e.g., before and after intervention). A *p*-value below 0.05 indicated a statistically

significant change. The Mann–Whitney U test was applied to compare the two independent groups; based on ranked data, it assesses whether values in one group are systematically higher or lower than those in the other. Finally, Spearman’s rank correlation coefficient was used to evaluate relationships between vitamin D levels and metabolic parameters. This method is appropriate for non-normally distributed data and is less sensitive to outliers.

For data analysis, two measurements were used for each patient: the first available measurement (baseline) and the last available measurement (final follow-up). Patients with missing values for either measurement were excluded from the respective analyses. No imputation methods were applied; only complete data pairs were analysed. After excluding patients with missing data, the analysis included 7 patients from Group A and 8 patients from Group B.

### 3.2 Baseline Comparability

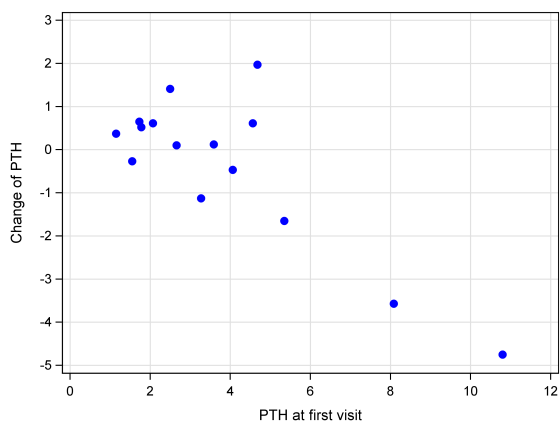
At baseline, all evaluated metabolic parameters were comparable in the high-dose (Group A) and lower-dose (Group B) vitamin D groups. There were no statistically significant between-group differences in PTH, HbA1c, FBG, calcium, phosphorus, or 25(OH)D (all *p* > 0.05, Wilcoxon rank-sum test) (Table 2).

Table 2 summarizes the changes in key metabolic parameters between the first and final visits for both groups. HbA1c levels remained relatively stable, with a slight decrease in Group A and a slight increase in Group B; however, these changes were not statistically significant, either within groups or between them. PTH levels decreased in Group A and increased in Group B, but none of these changes reached statistical significance. Similarly, glucose levels showed an upward trend in both groups, yet without statistical confirmation. Phosphorus and calcium levels remained essentially unchanged throughout the study in both

**Table 2. Descriptive statistics of metabolic parameters by group and visit, with paired and group comparison tests.**

Parameters	Descriptive statistics	Group A n = 7			Group B n = 8		
		First visit	Last visit	Change	First visit	Last visit	Change
HbA1C [%]	Mean (SD)	8.09 (1.7392)	7.66 (1.1907)	-0.43 (1.3306)	7.39 (0.3380)	7.88 (1.3230)	0.49 (1.3237)
	Median	7.600	7.480	-0.150	7.385	7.395	0.020
	Min; Max	6.43; 11.19	6.42; 9.70	-3.00; 1.23	7.01; 8.02	6.42; 10.33	-1.01; 3.20
	Q1; Q3	6.68; 9.44	6.53; 8.42	-1.02; 0.43	7.10; 7.56	7.07; 8.67	-0.29; 1.13
	<i>p</i> -value of paired test			0.5781			0.5469
	<i>p</i> -value of group comparison test						0.2243
PTH [pmol/L]	Mean (SD)	3.09 (1.4521)	2.67 (1.0434)	-0.42 (0.7335)	4.53 (3.3277)	4.21 (1.6809)	-0.32 (2.4437)
	Median	3.270	2.760	-0.270	3.530	4.210	0.610
	Min; Max	1.15; 5.35	1.28; 3.71	-1.65; 0.37	1.73; 10.80	2.30; 6.65	-4.75; 1.97
	Q1; Q3	1.55; 4.06	1.52; 3.70	-1.13; 0.12	1.93; 6.38	2.53; 5.61	-1.53; 1.03
	<i>p</i> -value of paired test			0.2969			0.7109
	<i>p</i> -value of group comparison test						0.1179
FBG [mmol/L]	Mean (SD)	7.57 (2.8819)	8.38 (1.2289)	0.81 (1.7883)	8.39 (1.3640)	9.76 (2.4168)	1.37 (1.9623)
	Median	6.630	7.760	1.090	8.715	9.720	0.775
	Min; Max	4.58; 12.90	6.95; 10.32	-2.58; 3.18	5.53; 9.91	6.10; 13.62	-1.15; 4.90
	Q1; Q3	5.56; 9.34	7.53; 9.64	0.30; 1.91	7.95; 9.20	8.31; 11.17	0.41; 2.42
	<i>p</i> -value of paired test			0.2188			0.1094
	<i>p</i> -value of group comparison test						0.9539
P [mmol/L]	Mean (SD)	1.06 (0.2491)	1.16 (0.1567)	0.11 (0.1489)	1.06 (0.2420)	1.19 (0.2291)	0.13 (0.2285)
	Median	1.100	1.150	0.070	1.090	1.145	0.200
	Min; Max	0.74; 1.34	0.94; 1.36	-0.04; 0.41	0.75; 1.37	0.80; 1.50	-0.28; 0.35
	Q1; Q3	0.78; 1.29	1.01; 1.30	0.01; 0.16	0.83; 1.27	1.08; 1.40	-0.04; 0.33
	<i>p</i> -value of paired test			0.0781			0.1953
	<i>p</i> -value of group comparison test						0.8168
Ca [mmol/L]	Mean (SD)	2.28 (0.0661)	2.61 (0.7529)	0.33 (0.7672)	2.25 (0.1177)	2.26 (0.1031)	0.01 (0.1117)
	Median	2.300	2.350	0.030	2.260	2.245	0.010
	Min; Max	2.16; 2.36	2.24; 4.31	-0.06; 2.06	2.08; 2.44	2.10; 2.45	-0.15; 0.16
	Q1; Q3	2.25; 2.32	2.27; 2.40	0; 0.16	2.17; 2.31	2.20; 2.31	-0.08; 0.09
	<i>p</i> -value of paired test			0.1563			0.8125
	<i>p</i> -value of group comparison test						0.3537
Vitamin D [ng/mL]	Mean (SD)	16.15 (6.6699)	36.34 (13.7101)	20.19 (11.2833)	17.03 (6.5143)	25.31 (6.7336)	8.29 (5.4640)
	Median	17.200	31.800	13.300	18.500	28.200	8.100
	Min; Max	4.24; 24.50	25.00; 64.40	11.20; 39.90	7.07; 26.40	14.70; 32.50	0.50; 17.60
	Q1; Q3	11.70; 20.60	26.60; 42.90	11.60; 30.16	11.97; 20.90	19.10; 30.35	4.45; 11.55
	<i>p</i> -value of paired test			0.0156			0.0078
	<i>p</i> -value of group comparison test						0.0150

Max, Maximum; Mean, Arithmetic mean; Min, Minimum; Q1, Lower quartile; Q3, Upper quartile; SD, Standard deviation; HbA1c, glycated haemoglobin; PTH, parathyroid hormone; FBG, fasting blood glucose. *p*-values were calculated using the Wilcoxon signed-rank test and the Mann-Whitney U test for group comparisons.



**Fig. 1. Scatterplot of PTH [pmol/L].**

groups. Minor variations in mean or median values were observed, but none were statistically significant, indicating stable mineral metabolism. In contrast, both groups showed significant increases in vitamin D levels, with a much greater and statistically significant rise observed in Group A. The between-group comparison confirmed a significant difference, clearly demonstrating the superior effectiveness of higher-dose vitamin D supplementation. In summary, aside from the expected and statistically significant increase in vitamin D levels—particularly in Group A—none of the other parameters showed meaningful or statistically significant changes. This suggests that while high-dose vitamin D effectively raises serum concentrations, its short-term impact on glycaemic and mineral markers in this cohort was limited. PTH levels are presented as a scatterplot in Fig. 1.

Results of statistical tests adjusted for baseline values did not differ from those obtained using the Wilcoxon signed-rank test and the Mann–Whitney U test. Therefore, the original test methods were retained to ensure consistency across the analysis.

The box plots reveal differences between Groups A and B across several metabolic parameters (Fig. 2). In Group A, HbA1c values showed greater variability throughout the study, but the median slightly decreased, suggesting a potential positive trend. In contrast, Group B displayed stable HbA1c values with low variability and virtually no change over time. PTH levels decreased in Group A, while they increased in Group B, indicating a potential beneficial effect of high-dose vitamin D on PTH suppression in the intervention group. Glucose levels in Group A showed a slight increase in the median over time, with values becoming more clustered, suggesting a narrowing distribution. Group B exhibited a similar trend, although the change was less pronounced. Phosphorus values were initially lower in Group A and increased over time with reduced variability, indicating stabilization. Conversely, Group B showed both an increase in phosphorus and greater variability at the final visit, reflecting a less consistent pat-

tern. Calcium levels remained stable in both groups, with minimal changes in median values and similar variability, reinforcing the safety of high-dose vitamin D and the absence of hypercalcemia. Finally, vitamin D levels rose substantially in Group A, with increases in both the median and variability, clearly reflecting the impact of high-dose supplementation. Group B also showed an increase, but the change was less pronounced and more uniform, supporting the greater efficacy of the higher-dose regimen.

### 3.3 Correlation Analysis

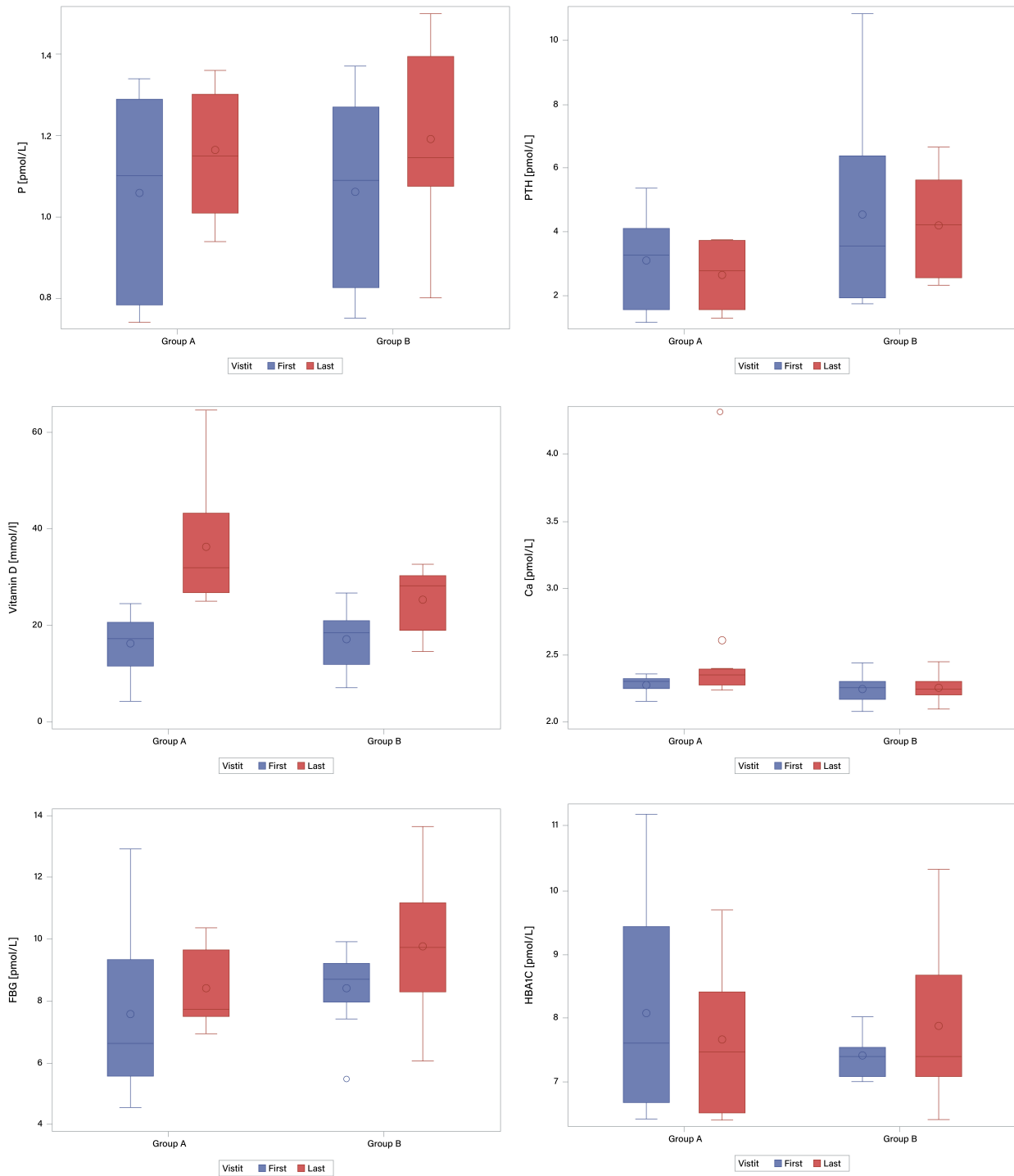
The correlation analysis examined relationships between changes in vitamin D levels and changes in selected parameters between the first and final patient visits. The strongest negative correlation was observed between the change in vitamin D and the change in PTH levels, with a greater increase in vitamin D associated with a decrease in PTH. This correlation was statistically significant ( $p = 0.0044$ ). Positive correlations between changes in vitamin D and changes in glucose and calcium levels suggest that higher increases in vitamin D may be associated with slight increases in glucose and calcium; however, these relationships were not statistically significant ( $p = 0.2287$  for glucose and  $p = 0.2554$  for calcium). Other parameters, such as phosphorus and HbA1c, showed only weak correlations with changes in vitamin D, none of which were statistically significant (Table 3). Overall, these findings indicate that changes in vitamin D levels were most strongly associated with changes in PTH, whereas associations with other metabolic parameters were less pronounced.

**Table 3. Correlation analysis of changes in parameter values and vitamin D levels between the first and final visit.**

Parameter	Spearman's correlation coefficient	$p$ -value
FBG	0.33065	0.2287
Calcium	0.31334	0.2554
HbA1C	-0.07685	0.7854
Phosphorus	-0.26009	0.3492
PTH	-0.69052	0.0044

The scatter plot confirms a negative correlation between changes in vitamin D levels and changes in PTH, visible as a downward trend in the corresponding panel (Fig. 3). Greater increases in vitamin D were associated with reductions in PTH levels, consistent with the results of Spearman's correlation coefficient and the observed statistical significance. A weak positive trend was noted for glucose and calcium, although the wide dispersion of data points indicates only a limited relationship. Phosphorus showed a slight negative correlation, while HbA1c values did not display any clear association with changes in vitamin D.

The aim of this study was to assess the effect of vitamin D supplementation on selected metabolic parameters—



**Fig. 2.** Box plots of baseline and 12-week values of metabolic parameters in the high-dose (Group A,  $n = 7$ ) and lower-dose (Group B,  $n = 8$ ) vitamin D groups. 25(OH)D increased significantly in both groups, with a greater increase in the high-dose group ( $p < 0.05$  for within-group and between-group comparisons). PTH showed only a modest change, without a statistically significant between-group difference. No statistically significant within-group or between-group differences were observed for HbA1c, FBG, calcium or phosphorus (all  $p > 0.05$ ).

specifically PTH, glucose, calcium, phosphorus, and HbA1c—and to explore their relationship with changes in vitamin D levels. Patients were divided into an intervention group (Group A) and a control group (Group

B), with changes tracked between the first and final visits. Parameter-specific analysis revealed that vitamin D supplementation had the strongest effect on PTH levels. A statistically significant negative correlation was observed, indicat-

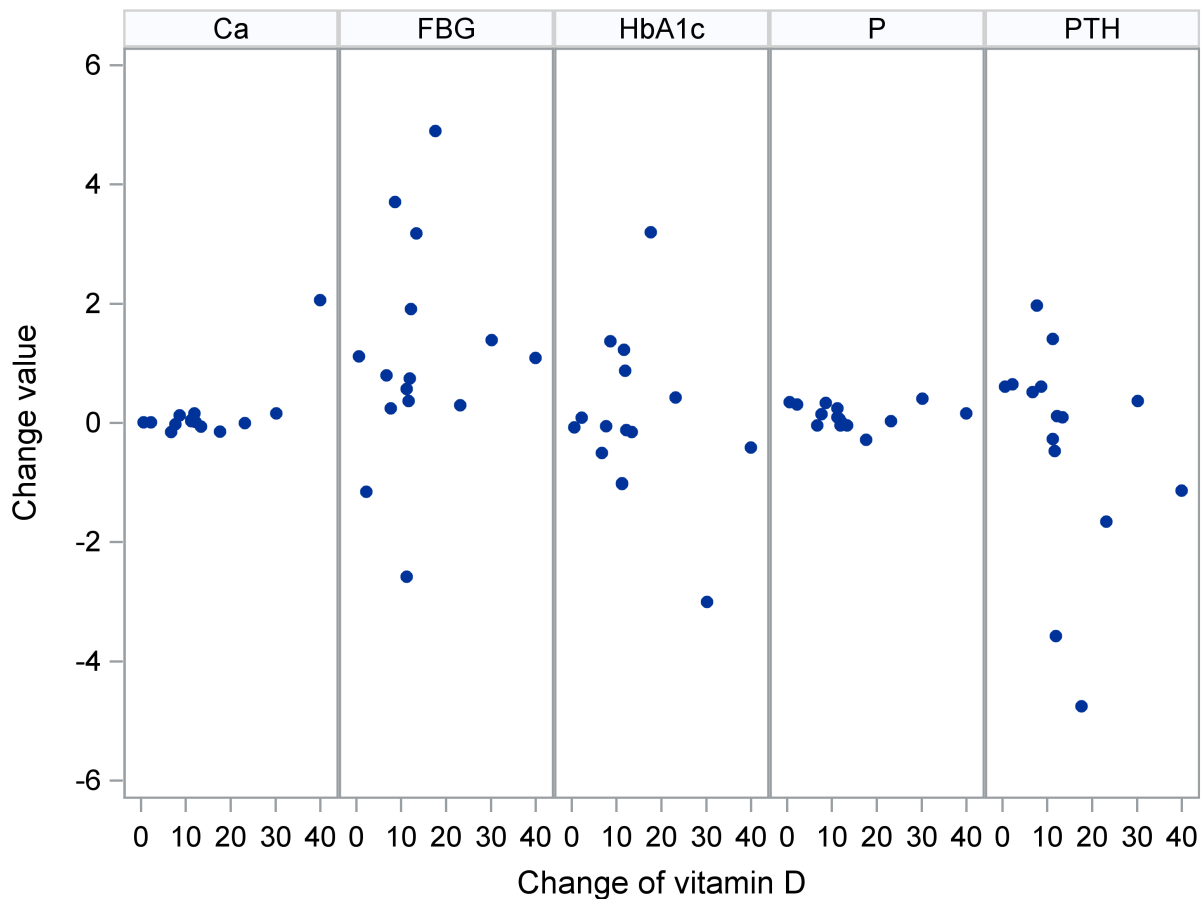


Fig. 3. Scatter plots – change in parameters vs. change in vitamin D.

ing that rising vitamin D levels were associated with reductions in PTH. In contrast, no statistically significant changes or correlations were observed for glucose, calcium, phosphorus, or HbA1c. Glucose levels showed a slight increase in both groups, but this was not statistically significant, suggesting that vitamin D supplementation does not directly affect glycaemic control over the observed period. Calcium and phosphorus levels remained stable, with no relevant changes or group differences. Similarly, HbA1c levels did not differ significantly, indicating that short-term vitamin D supplementation does not influence long-term glucose regulation. In summary, vitamin D supplementation had the most pronounced and statistically significant impact on PTH levels. Other metabolic parameters remained largely unchanged, suggesting that the primary short-term effect of high-dose vitamin D lies in bone metabolism and parathyroid regulation. Effects on other metabolic markers may require longer follow-up or larger sample sizes to be reliably detected.

#### 4. Discussion

According to current scientific data, approximately 40% of the European population has insufficient vitamin D levels, defined as serum 25(OH)D concentrations below

20 ng/mL [24]. This represents a significant public health concern, as low vitamin D levels are associated with an increased risk of numerous health complications, including impaired bone health, immune dysfunction, greater susceptibility to infections, and a higher risk of chronic diseases such as type 2 diabetes, cardiovascular disease, and certain cancers [25]. Even more concerning, about 13% of the European population is affected by severe vitamin D deficiency—defined as serum levels below 12 ng/mL—which may substantially impair health and quality of life [26]. These statistics highlight the urgent need to implement effective and targeted vitamin D supplementation strategies on a population-wide scale. Supplementation is particularly important in high-risk groups that are more vulnerable to the adverse consequences of deficiency, including older adults with reduced cutaneous vitamin D synthesis and individuals with prediabetes or type 2 diabetes, in whom deficiency may exacerbate insulin resistance and accelerate disease progression. People with elevated BMI are also disproportionately affected, as adipose tissue sequesters vitamin D and reduces its bioavailability [27,28].

In this context, increased attention should be directed toward targeted vitamin D supplementation strategies tailored to the individual needs and risk factors of specific pop-

ulations. Effectively addressing widespread deficiency requires a multidisciplinary approach that includes public and professional education on appropriate supplementation and the implementation of preventive and interventional programs focused on routine vitamin D monitoring, particularly in high-risk groups. Such efforts could substantially mitigate the negative public health impact of vitamin D deficiency and improve quality of life at a population level.

From a clinical perspective, one of the key ongoing questions is determining the optimal dosing of vitamin D necessary to achieve and maintain sufficient serum concentrations. Although current international guidelines provide clear recommendations, clinical practice continues to encounter inconsistencies and debate regarding individualized dosing.

The Endocrine Society, a leading authority in endocrinology and vitamin D metabolism, currently recommends daily doses between 800 and 2000 IU for most healthy adults to maintain adequate serum 25(OH)D levels. These recommendations consider physiological needs and cutaneous synthesis from sunlight exposure. Standard supplementation is effective in preventing deficiency in the general population, particularly among individuals with limited but regular sun exposure [29]. However, in clinical practice, it is often necessary to rapidly and effectively correct severe vitamin D deficiency, typically defined as serum 25(OH)D levels below 12 ng/mL. In such cases—where the goal is rapid repletion and resolution of clinical symptoms—the Endocrine Society guidelines allow for short-term administration of higher doses, such as 6000 IU per day or more, depending on clinical context [30]. Clinical studies have consistently shown that these high doses effectively raise serum vitamin D levels to optimal ranges and may lead to prompt clinical improvement. Although high doses of vitamin D (typically above 4000 IU daily) are effective in correcting deficiency [31], concerns remain about their long-term safety, particularly regarding the risk of overdose. Prolonged high-dose use, especially without monitoring, may result in adverse effects such as hypercalcemia, nephrocalcinosis, or soft tissue calcification [32,33]. For this reason, most clinical guidelines emphasize that after successful correction of deficiency with high doses, patients should transition to lower maintenance doses appropriate for long-term supplementation [34]. These maintenance doses—generally between 800 and 2000 IU daily—are adequate for sustaining vitamin D stability without risking excessive accumulation. Dosing should always be individualized based on factors such as age, body weight, sun exposure, comorbidities, concurrent medications, and ongoing monitoring of serum 25(OH)D levels to ensure both safety and effectiveness [30].

Such a personalized and comprehensive approach enables clinicians to use vitamin D safely while minimizing the risks associated with improper or excessive dosing. It also provides flexibility in addressing diverse patient needs

and supports both prevention and treatment of vitamin D deficiency at individual and population levels.

Our biomedical study aimed to build upon existing evidence by evaluating the effects of vitamin D supplementation under real-world clinical conditions. We monitored changes in serum vitamin D concentrations and their impact on metabolic parameters, patient-reported quality of life, and treatment satisfaction. Our findings confirmed a statistically significant negative correlation between vitamin D and PTH levels, indicating a robust inverse relationship. This observation is consistent with mechanistic evidence and supports the clinical validity of our hypothesis.

In contrast, we did not observe significant changes in HbA1c, FBG, serum calcium, or phosphorus levels. These findings align with previously reported data summarized in our systematic review and suggest that vitamin D supplementation may not induce short-term improvements in glycaemic or mineral metabolism. The small, non-significant increase in blood glucose observed in both study groups further supports the notion that vitamin D is unlikely to influence glycaemic control over a short observation period. Similarly, the stability of HbA1c, calcium, and phosphorus values suggests that longer intervention periods, alternative dosing strategies, or larger sample sizes may be necessary to detect meaningful metabolic effects.

Overall, our results contribute valuable real-world data to the growing body of evidence on vitamin D supplementation in individuals with type 2 diabetes mellitus (T2DM). The findings emphasize the need for longer-term, adequately powered trials to clarify the potential metabolic benefits of vitamin D. They also underscore the importance of individualized therapeutic strategies in diabetes care and highlight the necessity for continued investigation into the broader metabolic role of vitamin D.

## 5. Conclusions

The results of our biomedical study support the safety and efficacy of high-dose vitamin D supplementation (>4000 IU/day) in achieving optimal serum 25(OH)D concentrations without evidence of hypervitaminosis or hypercalcemia. A significant reduction in PTH levels was observed in the intervention group, with a strong negative correlation between changes in vitamin D and PTH levels, highlighting a clear effect on calcium metabolism and bone health. No statistically significant changes were found in HbA1c, FBG, serum calcium, or phosphorus, suggesting that short-term high-dose vitamin D supplementation has limited metabolic impact beyond PTH regulation. A slight, non-significant increase in FBG was observed in both study groups, indicating that the effect of vitamin D on glycaemic control may be modest and not immediate. Taken together, our findings suggest that the primary clinical benefit of high-dose vitamin D supplementation in patients with type 2 diabetes lies in correcting vitamin D deficiency and reducing PTH levels rather than improving glycaemic parameters.

Further studies with longer follow-up periods and larger cohorts are warranted to better evaluate long-term metabolic effects and patient-reported outcomes.

### Availability of Data and Materials

The datasets generated and analyzed during the current study are not publicly available due to patient confidentiality, but are available from the corresponding author upon reasonable request.

### Author Contributions

Conceptualization, FM, AG, TT and JP; methodology, FM, PJ, MK, JP and JK; software, PJ and MK; validation, AG, TT and JP; formal analysis, FM, AG, DD, JS, MJ and JP; investigation, JS, DD, MJ; resources, AG and TT; data curation, FM, AG and JP; writing—original draft preparation, FM; writing—review and editing, FM, AG and TT; visualization, FM; supervision, FM, AG, TT and JP; project administration, FM, AG, TT and JP; funding acquisition, FM and TT. All authors have read and agreed to the published version of the manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

### Ethics Approval and Consent to Participate

Ethics approval for this study was obtained from the Ethics Committee of the University Hospital Bratislava – Ružinov (reference EK/041/2022, March 23, 2022). All participants provided written informed consent before participation. The authors confirm that all experimental protocols were approved by the Ethics Committee of the University Hospital Bratislava – Ružinov. The study is conducted in compliance with the Declaration of Helsinki of the World Medical Association—Ethical Principles for Medical Research Involving Human Subjects.

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### Conflict of Interest

The authors declare no conflict of interest.

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