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Changes in the enamel surface in patients with polymorphism of the *VDR* gene under the action of remineralizing composition and vitamin D

Svetlana N. Tikhonova[1], Marina V. Kozlova[1], Ekaterina A. Gorbatova[1], Oksana L. Evstafyeva[2]

[1] Central State Medical Academy at the Department of Presidential Affairs of the Russian Federation, Moscow, Russia;
[2] Russian University of Medicine, Moscow, Russia

ABSTRACT

BACKGROUND: The leading role in the pathogenetic mechanism of caries development is the imbalance between the de and remineralization of hard tooth tissues. The combination of *VDR* alleles affects calcium-phosphate metabolism. In 65% of the human population, the structure of the *VDR* gene has a genetic polymorphism.

AIM: To study the effect of vitamin D and a remineralizing paste on the enamel surface structure in patients with genetic polymorphism of VDR gene receptors.

***MATERIALS AND METHODS*:** In 18 individuals with a polymorphism index of the *VDR* A/A gene, a laboratory indicator of 25 (OH) vitamin D in the blood of 18.20±1.84 ng/ml, according to orthodontic indications, the retinated third molars in the lower jaw were removed. Then, the samples were lowered into three flasks of six pieces with 100 ml of artificial saliva. Containers with teeth were divided into groups: group 1, with a solution of artificial saliva only; group 2, an additional 1,000 IU of an aqueous solution of vitamin D; and group 3, tooth enamel was treated for 2 minutes with an electric toothbrush with a paste containing a remineralizing composition, immersed in artificial saliva with cholecalciferol 1,000 IU. The flasks were in the thermostat at a temperature of 37.4 C per day. In all samples, electron microscopy of the enamel contact surface at the level of the crown equator was performed using a Tescan Mira 3 LMU microscope (TESCAN, Czech Republic) with an Oxford X-MAX 5 energy dispersive X-ray detector (Oxford Instruments, United Kingdom) with analysis of local mineral composition.

RESULTS: In group 1, with electron microscopy of enamel, areas of increased mineralization alternated with areas of reduced density. The coefficient of the molar ratio Ca/P was 1.32±0.13, indicating the destruction of hydroxyapatites. In group 2 the intercrystalline pore space was filled with calcium and phosphate ions. In group 3, the enamel surface acquired a smooth homogeneous relief. An increase in the weight percentage of trace elements was observed, and the Ca/P ratio was 2.20±0.02, which indicated a phase of remineralization.

CONCLUSION: Patients with *VDR* gene polymorphism have a vitamin D deficiency in the blood serum. The trace element composition of the enamel surface is characterized by a phase of demineralization. Treatment with remineralizing paste and addition of cholecalciferol solution to artificial saliva changes the structure of hydroxyapatite and increases the caries-resistant properties of enamel.

Keywords: tooth enamel structure; *VDR* gene receptor polymorphism; vitamin D; mineral composition of tooth enamel.

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Влияние витамина D и реминерализирующей пасты на поверхность эмали у пациентов с полиморфизмом гена *VDR*

С.Н. Тихонова[1], М.В. Козлова[1], Е.А. Горбатова[1], О.Л. Евстафьева[2]

[1] Центральная государственная медицинская академия Управления делами Президента, Москва, Россия;
[2] Российский университет медицины, Москва, Россия

АННОТАЦИЯ

Обоснование. Ведущую роль в патогенетическом механизме развития кариеса отводят нарушению равновесия между процессами де- и реминерализации твёрдых тканей зуба. Сочетание аллелей гена *VDR* влияет на кальциево-фосфатный метаболизм. У 65% людей структура гена *VDR* имеет генетический полиморфизм.

Цель исследования — изучить влияние витамина D и зубной пасты с реминерализирующим составом на структуру поверхности эмали у пациентов с генетическим полиморфизмом рецепторов гена *VDR*.

Материалы и методы. У 18 человек с показателем полиморфизма гена *VDR* A/A и лабораторным показателем 25(OH) витамина D в крови 18,20±1,84 нг/мл по ортодонтическим показаниям удаляли ретинированные третьи моляры нижней челюсти. Далее удалённые зубы по 6 штук опускали в 3 колбы со 100 мл искусственной слюны и разделяли на группы: первая — с раствором только искусственной слюны; вторая — дополнительно с 1000 МЕ водного раствора витамина D; в третьей группе эмаль зубов обрабатывали в течение 2 мин электрической зубной щёткой с пастой, содержащей реминерализирующий состав, затем погружали в искусственную слюну с холекальциферолом (1000 МЕ). Колбы в течение суток находились в термостате при температуре 37,4 °C. Для всех образцов проводили электронную микроскопию контактной поверхности эмали на уровне экватора коронки с помощью микроскопа Tescan Mira 3 LMU (TESCAN, Чехия) с энергодисперсионным рентгеновским детектором X-MAX 5 (Oxford Instruments, Великобритания) для анализа локального минерального состава.

Результаты. В первой группе при электронной микроскопии эмали установлено, что участки повышенной минерализации чередовались с зонами пониженной плотности. Коэффициент молярного соотношения Ca/P составил 1,32±0,13, расценивался как деструкция гидроксиапатитов. Во второй группе межкристаллическое пространство пор заполняли ионы кальция и фосфата. В третьей группе поверхность эмали приобретала ровный однородный рельеф. Наблюдали увеличение весового процента микроэлементов, соотношение Ca/P составляло 2,20±0,02, что свидетельствовало о фазе реминерализации.

Заключение. *У* пациентов с полиморфизмом гена *VDR* наблюдается дефицит витамина D в сыворотке крови. Микроэлементный состав поверхности эмали характеризуется фазой деминерализации. Обработка реминерализирующей пастой и добавление к искусственной слюне раствора холекальциферола изменяют структуру гидроксиапатита, повышают кариесрезистентные свойства эмали.

Ключевые слова: структура эмали зуба; полиморфизм рецепторов гена *VDR*; витамин D; минеральный состав эмали зуба.

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BACKGROUND

In various regions of the Russian Federation, dental caries is diagnosed in 60% to 98% of the adult population [1]. Over the past decades, despite the development of modern preventive and diagnostic approaches, the prevalence of this condition has not declined [2].

The leading pathogenetic mechanism in the development of caries is an imbalance between demineralization and remineralization processes of dental hard tissues. The most widely recognized parameter for assessing enamel status is the molar calcium-to-phosphate ratio (Ca/P), considered optimal at 1.67 [3]. Under conditions of increased enamel permeability, calcium ions may be replaced by chemically similar elements, altering the Ca/P ratio and thereby modifying the physicochemical properties of enamel crystals [4–6]. Enamel resistance to acid dissolution and destruction increases in direct proportion to the Ca/P ratio.

The balance between demineralization and remineralization processes in dental hard tissues depends on numerous local and systemic factors. Several publications have demonstrated a correlation between vitamin D receptor (*VDR*) gene polymorphisms and mineral metabolism [7–10].

In recent decades, it has been established that $1,25(OH)_2$ D3 (calcitriol) acts as a ligand for VDR, binding to it and regulating bone mineral density. The D3–VDR hormone–receptor complex activates the synthesis of calcium-binding protein, facilitates the transmembrane transport of Ca^{2+} into the cytoplasm, and mobilizes calcium from intracellular stores [11]. Specific allele combinations of the *VDR* gene affect calcium-phosphate metabolism [10]. Approximately 65% of individuals demonstrate genetic polymorphism in VDR structure [12].

Investigating the effect of vitamin D on the structure and composition of dental hard tissues in individuals with *VDR* gene polymorphisms is of both scientific and clinical importance.

This work aimed to assess the effect of vitamin D and a remineralizing toothpaste on enamel surface structure in patients with genetic polymorphisms of the *VDR* gene.

MATERIALS AND METHODS

Study Design

This investigation was designed as an experimental, multicenter, prospective, continuous, controlled, randomized study (Fig. 1).

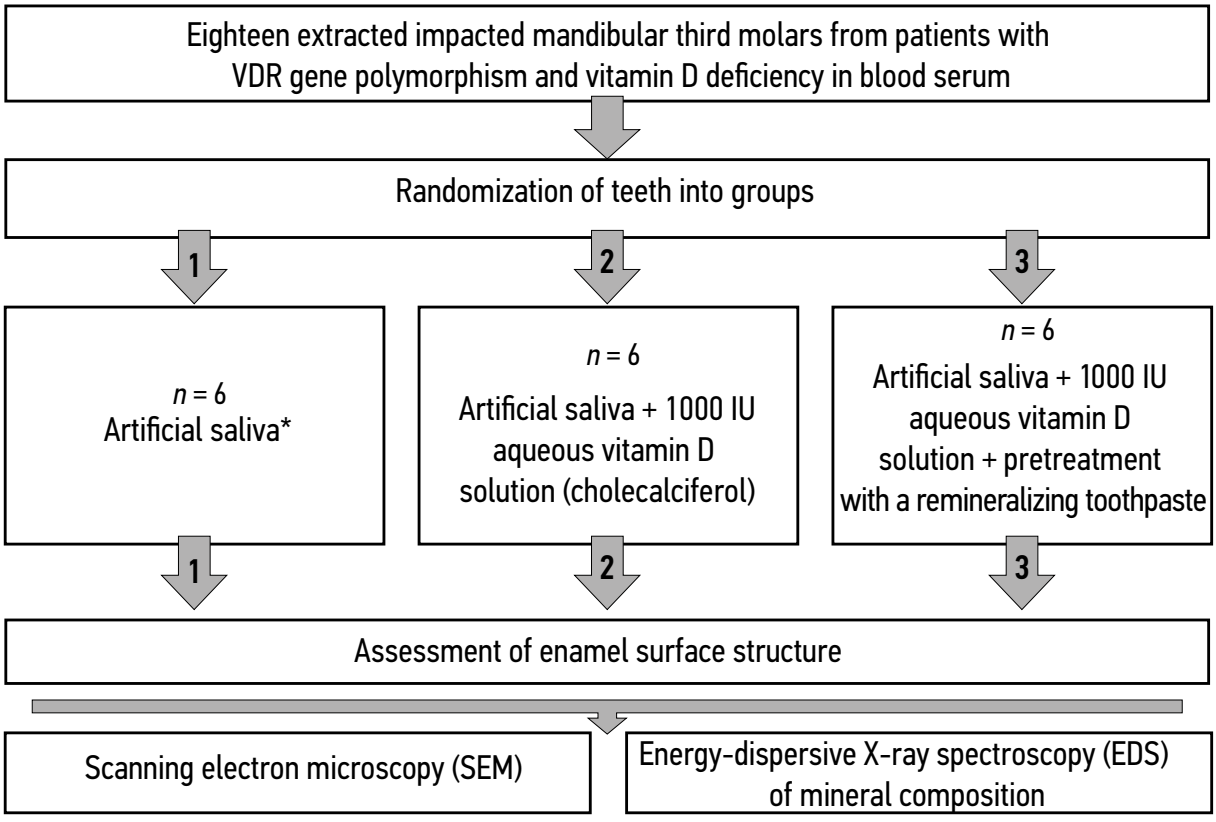

Fig. 1. Study design. *Composition of artificial saliva: structured water; electrolytes (Na^+, 0.3 g/L; K^+, 1.0 g/L; Ca^{2+}, 0.05 g/L; Mg^{2+}, 0.01 g/L; Cl^-, 0.1 g/L; $(PO_4)^{3-}$, 0.1 g/L); organic components (0.5% carboxymethylcellulose, alginic acid, urea).

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Study Setting

The study was conducted in 2023 at the Department of Dentistry, Central State Medical Academy of the Administrative Directorate of the President of the Russian Federation, and included both a clinical stage and an experimental stage at the Laboratory of the Technological Institute for Superhard and Novel Carbon Materials (Russian Academy of Sciences).

Intervention

A total of 100 patients aged 25 to 30 years, who self-identified as practically healthy, were examined during routine dental visits (dental prophylaxis). All participants were residents of Moscow and the Moscow region and had a history of regular dental care. Each patient underwent genetic testing for the vitamin D receptor (*VDR*) gene.

Based on genotyping results, a study cohort of 18 patients (6 men and 12 women; mean age, 26.0 ± 2.48 years) with *VDR* polymorphism A/A (homozygous state, indicating a marked reduction in receptor expression) was selected. The simplified oral hygiene index (OHI-S) averaged 1.12 ± 0.04, consistent with a satisfactory level of oral hygiene. The DMFT index was 12.8 ± 0.04, which corresponds to a high caries intensity. Caries prevalence in the group was 45.0 ± 0.05. Serum 25(OH)D levels averaged 18.2 ± 1.84 ng/mL, consistent with vitamin D deficiency.

For orthodontic indications, all 18 patients with A/A polymorphism underwent surgical extraction of impacted mandibular third molars. Extracted teeth had intact anatomic structure and showed no evidence of carious lesions.

During the experimental phase, the 18 extracted teeth were divided into 3 groups of 6 specimens each. Each group was immersed in 100 mL of artificial saliva containing structured water; electrolytes (Na^+, 0.3 g/L; K^+, 1 g/L; Ca^{2+}, 0.05 g/L; Mg^{2+}, 0.01 g/L; Cl^-, 0.1 g/L; PO_4^{3-}, 0.1 g/L); and organic components (0.5% carboxymethylcellulose, alginic acid, and urea).

The groups were prepared as follows:

- Group 1: Immersion in artificial saliva only.
- Group 2: Artificial saliva with an additional 1000 IU of aqueous vitamin D solution [13].
- Group 3: Enamel surfaces were first brushed for 2 minutes with an electric toothbrush and a remineralizing toothpaste, then immersed in artificial saliva supplemented with 1000 IU cholecalciferol.

The flasks with specimens were placed in a laboratory dry-air thermostat at 37.4 °C for 24 hours. Following incubation, the teeth were rinsed under running water for 30 seconds.

Outcomes Registration

In each group, scanning electron microscopy (SEM) of the enamel contact surface at the tooth equator was performed using a Tescan Mira 3 LMU microscope (TESCAN, Czech Republic) equipped with an X-MAX 5 energy-dispersive X-ray detector (Oxford Instruments, UK) (Fig. 2).

For morphological evaluation, specimens were placed in the SEM vacuum chamber under conditions of < 90 × 10^{-3} Pa. The accelerating voltage and probe currents applied during surface examination were 1 kV and 0.1–1 nA, respectively. Fields of 20 mm were scanned in topographic (secondary electron, SE) and compositional (backscattered electron, BSE) contrast modes at magnifications corresponding to scales of 100 μm, 20 μm, and 5 μm.

Analysis of the localized mineral composition of enamel surfaces was carried out by energy-dispersive X-ray spectroscopy (EDS). Measurements were performed with probe currents of approximately 20 nA and an accelerating voltage of 13 kV. Atomic and weight percentages were determined using a standardless EDS method with INCA Point & ID software (Oxford Instruments) following quantitative optimization of probe current against a silicon standard at 13 kV.

Ethics Approval

All patients included in the study provided written informed consent for the surgical extraction of impacted mandibular third molars in accordance with Order No. 390n of the Ministry of Health and Social Development of the Russian Federation of April 23, 2012 and Article 20 of Federal Law No. 323 of November 21, 2011.

Fig. 2. TESCAN Mira 3 LMU scanning electron microscope (TESCAN, Czech Republic).

Statistical Analysis

All results were processed using methods of biomedical statistics. Mean values are presented as M ± m, where M indicates the arithmetic mean and m the standard error of the mean. Statistical significance was accepted at $p \leqslant 0.05$.

Data processing was performed using Microsoft Excel (Microsoft Corp) for descriptive statistics, and intergroup comparisons of independent samples were conducted with SPSS software (IBM Corp).

RESULTS

Primary Results

In all tooth specimens of the first group (patients with vitamin D deficiency in blood plasma), SEM images at a scale of 100 μm revealed enamel represented by a regular undulating structure formed by perikymata. Areas of increased mineralization alternated with zones of reduced density exhibiting a characteristic honeycomb-like pattern. Depressions of varying size were observed on the enamel surface (Fig. 3, *a*).

At a scale of 20 μm, enamel prisms consisting of densely packed hydroxyapatite crystals were visualized as a smooth surface with lacunae of rounded shape, variable size, and depth (Fig. 3, *b*). At a magnification corresponding to a 5-μm scale bar, distinct intercrystalline pores were observed within hypomineralized bands, which formed interprismatic spaces filled with fluid (Fig. 3c).

Structural analysis of the mineral composition of enamel in retained third molars is presented in Table 1. The molar calcium-to-phosphate (Ca/P) ratio was 1.32 ± 0.13.

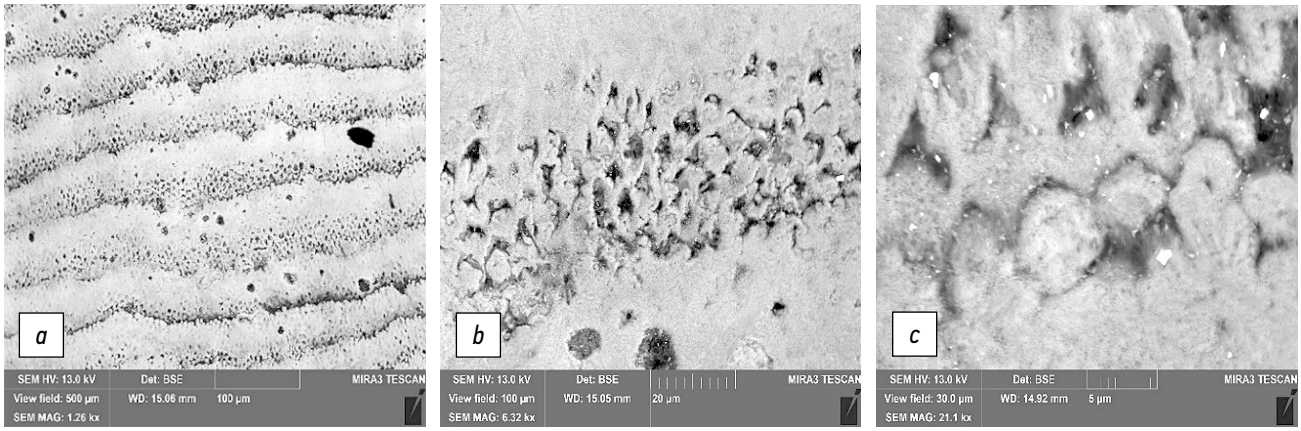

Fig. 3. Scanning electron microscopy of enamel samples from teeth of patients in Group 1 with vitamin D deficiency and *VDR* gene polymorphism: *a*, magnification ×100 μm; *b*, magnification ×20 μm; *c*, magnification ×5 μm.

Table 1. Structural analysis of the weight percentage of trace element composition of the tooth enamel surface

Element	Weight percentage of microelements, %				
	Group 1 (*n* = 6)	Group 2 (*n* = 6)	*p*	Group 3 (*n* = 6)	*p*
Mg^{2+}	0.11±0.02	0.18±0.02	0.035	0.18±0.02	0.035
Na^{+}	0.72±0.05	0.55±0.05	0.039	0.35±0.04	0.002
Si^{4+}	0.24±0.04	0.25±0.03	0.07	0.51±0.05	0.002
P^{3+}	10.65±0.22	14.65±0.72	0.002	18.16±1.96	0.004
Cl^{-}	0.26±0.04	0.37±0.02	0.036	0.48±0.05	0.003
Ca^{2+}	14.05±1.72	20.61±1.38	0.001	39.95±1.98	0.001
Ca/P	1.32±0.13	1.41±0.02	0.512	2.21±0.02	0.003

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In the Group 2 (teeth immersed in artificial saliva supplemented with vitamin D), SEM images of enamel at a 100 μm scale demonstrated preservation of the undulating perikymata pattern, with increased width. The enamel surface appeared smoother, with a faint honeycomb appearance (Fig. 4*a*).

At a magnification corresponding to a 20-μm scale bar, enamel prism heads were elevated above the surface, while the intercrystalline pore spaces appeared smoothed out (Fig. 4, *b*). At higher magnification corresponding to a 5-μm scale bar, changes in enamel surface structure were clearly visualized, with reductions in both the number and the size of intercrystalline voids (Fig. 4 *c*).

Elemental analysis of enamel surfaces exposed to vitamin D demonstrated increased weight percentages of Ca^{2+}, Mg^{2+}, Cl^{-}, and $(PO_4)^{3-}$ ($p < 0.05$). The Ca/P ratio increased to 1.41 ± 0.02 (Table 1).

In the Group 3 (teeth treated with cholecalciferol and a remineralizing toothpaste containing calcium and phosphate complexes), SEM images at a scale of 100 μm revealed structural changes in enamel. The surface acquired a smooth, homogeneous relief due to flattening of the perikymata (Fig. 5, *a*).

At a scale of 20 μm, interprismatic spaces were filled with mineral components (Fig. 5, *b*). At a scale of 5 μm, enamel prism heads were elevated above the surface and displayed a smooth, gradual contour. The interprismatic spaces were sealed by minerals and visualized as shallow depressions (Fig. 5, *c*).

Elemental analysis indicated a statistically significant increase in weight percentages of $(PO_4)^{3-}$ and Si^{4+} by 2-fold, Ca^{2+} by 3-fold, and a 1.7-fold increase in the Ca/P ratio (2.21 ± 0.02) ($p < 0.05$). A significant 2-fold reduction in Na^{+} weight percentage was also observed relative to the Group 1 ($p < 0.05$) (Table 1).

DISCUSSION

In the Group 1, structural analysis of the mineral composition of the enamel surface of impacted molars

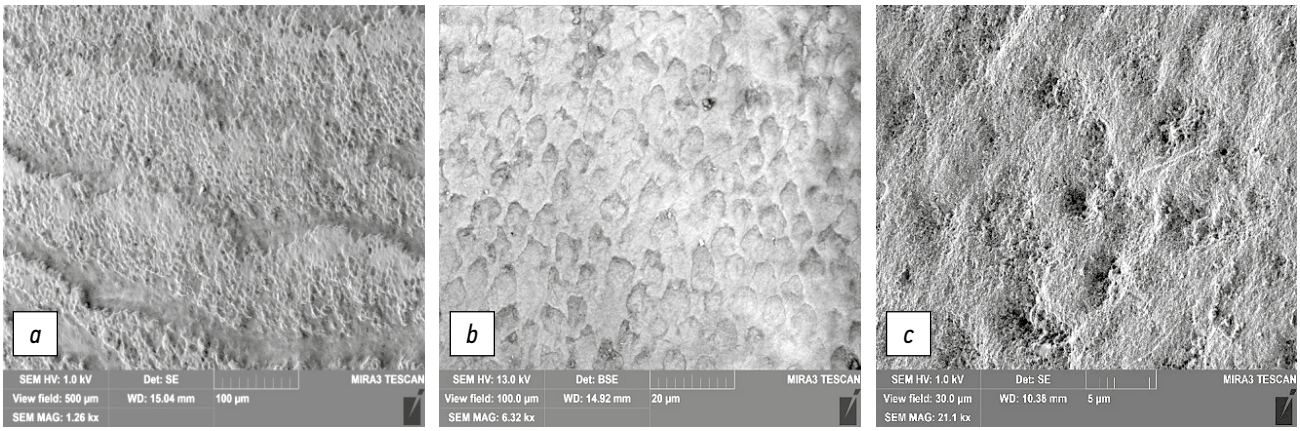

Fig. 4. Scanning electron microscopy of enamel samples from teeth of patients in Group 2 with *VDR* gene polymorphism after exposure to vitamin D solution: *a*, magnification ×100 μm; *b*, magnification ×20 μm; *c*, magnification ×5 μm.

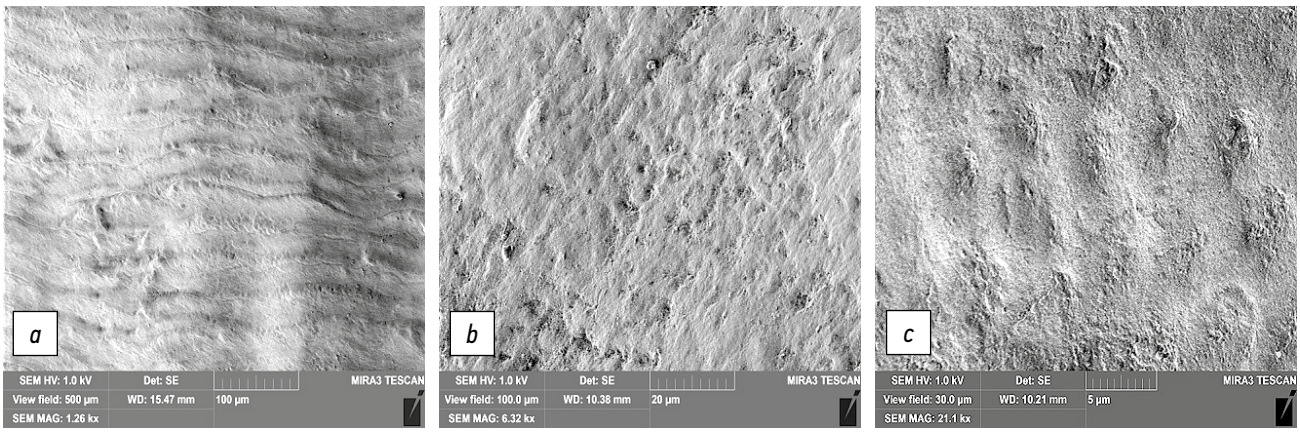

Fig. 5. Scanning electron microscopy of enamel samples from teeth of patients in Group 3 with *VDR* gene polymorphism after exposure to vitamin D solution and remineralizing toothpaste: *a*, magnification ×100 μm; *b*, magnification ×20 μm; *c*, magnification ×5 μm.

in patients with *VDR* polymorphism and plasma vitamin D deficiency revealed changes attributable to metabolic processes in the surrounding bone tissue. It is well established that the degree of enamel mineralization depends on the weight fraction of key macroelements, such as calcium and phosphate. Their weight percentages in enamel samples of the Group 1 were reduced compared with reported values in patients without vitamin D deficiency [14]. The Ca/P molar ratio, which reflects the balance between enamel demineralization and remineralization, was 1.32 ± 0.13. According to previous authors [3, 6], this ratio should be interpreted as indicative of hydroxyapatite crystal degradation.

In the Group 2, lacunae of interprismatic fluid became saturated with calcium and phosphate ions. The transport of these ions occurred along a concentration gradient from the artificial saliva in the presence of cholecalciferol. It is plausible that vitamin D facilitated the binding of these ions with phosphate complexes present in the medium, leading to hydroxyapatite formation. The resulting complexes appeared to partially fill the interprismatic voids. These metabolic processes produced only minor changes in the Ca/P ratio, which nevertheless did not reach the optimal value.

In the Group 3, additional treatment of retained third molars with remineralizing toothpaste and the presence of cholecalciferol in the artificial saliva led to saturation of enamel surfaces with calcium-phosphate ions. In all SEM imaging modes, enamel exhibited a smooth, homogeneous relief.

The increase in weight percentages of Ca^{2+}, $(PO_4)^{3-}$, and Si^{4+}, along with the elevated Ca/P ratio (2.20 ± 0.02), indicated an active phase of remineralization. The reduction in sodium content within enamel structure was explained by isomorphic substitution with Ca^{2+} ions. Due to their larger atomic radius, Ca^{2+} ions confer competitive advantages in metabolic exchange, thereby strengthening hydroxyapatite crystal lattice structure and improving mechanical resistance.

CONCLUSION

In patients with VDR receptor polymorphism, vitamin D deficiency in serum was associated with altered metabolism in bone tissue surrounding retained teeth and with changes in enamel surface structure. The mineral composition of enamel was characterized by predominance of demineralization processes, which underlie the pathogenesis of dental caries.

Treatment of enamel surfaces with a calcium-phosphate–containing toothpaste and supplementation of artificial saliva with cholecalciferol created favorable conditions for strengthening the hydroxyapatite crystal lattice and enhancing the caries-resistance properties of enamel.

ADDITIONAL INFORMATION

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Author contributions: S.N. Tikhonov—collection and analysis of literary sources, conducting the experimental part of the study, preparing and writing the text of the article; M.V. Kozlova—idea and design of the study, surgical treatment of patients participating in the study, editing the text of the article; E.A. Gorbatova—analysis of literary sources, writing and editing the text of the article; O.L. Evstafieva—editing the text of the article. All authors affirm their compliance with the international ICMJE criteria (all authors made substantial contributions to the conceptualization, research, and manuscript preparation, and reviewed and approved the final version prior to publication).

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AUTHORS' INFO

*** Svetlana N. Tikhonova;**
address: 19 bldg, 1a Marshal Timoshenko street, 121359 Moscow, Russia;
ORCID: 0009-0004-7372-8833;
eLibrary SPIN: 6610-7509;
e-mail: tixonovalana@gmail.com

Marina V. Kozlova, MD, Dr. Sci. (Medicine), Professor;
ORCID: 0000-0002-3066-206X;
eLibrary SPIN: 5546-2489;
e-mail: profkoz@mail.ru

Ekaterina A. Gorbatova, MD, Cand. Sci. (Medicine), Associate Professor;
ORCID: 0000-0002-7729-7979;
eLibrary SPIN: 5836-2399;
e-mail: gorbatova_k@mail.ru

Oksana L. Evstafyeva, MD, Cand. Sci. (Medicine), Associate Professor;
ORCID: 0000-0003-2358-0557;
eLibrary SPIN: 5455-8875;
e-mail: evstafieva_ol@mail.ru

* Corresponding author / Автор, ответственный за переписку

ОБ АВТОРАХ

*** Тихонова Светлана Николаевна;**
адрес: Россия, 121359, Москва, ул. Маршала Тимошенко, д. 19, стр. 1а;
ORCID: 0009-0004-7372-8833;
eLibrary SPIN: 6610-7509;
e-mail: tixonovalana@gmail.com

Козлова Марина Владленовна, д-р мед. наук, профессор;
ORCID: 0000-0002-3066-206X;
eLibrary SPIN: 5546-2489;
e-mail: profkoz@mail.ru

Горбатова Екатерина Александровна, канд. мед. наук, доцент;
ORCID: 0000-0002-7729-7979;
eLibrary SPIN: 5836-2399;
e-mail: gorbatova_k@mail.ru

Евстафьева Оксана Леонидовна, канд. мед. наук, доцент;
ORCID: 0000-0003-2358-0557;
eLibrary SPIN: 5455-8875;
e-mail: evstafieva_ol@mail.ru