Original Article
http://dx.doi.org/10.1590/1678-7757-2022-0335

JAOS
JOURNAL OF APPLIED ORAL SCIENCE

Treatment of chronic generalized periodontitis in patients with underlying hypovitaminosis D: randomized comparative clinical trial

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Abstract

Objectives: This study aims to evaluate the dynamics of clinical and laboratory indicators of the periodontal state and hemodynamics in patients receiving pharmaceutical intervention for the treatment of vitamin D deficiency as a part of the complex therapy of chronic generalized periodontitis. Methodology: This was a randomized prospective comparative clinical trial. It involved 110 patients with moderate generalized periodontitis and vitamin D deficiency (25(OH)<50 nmol/L) who were divided into two experimental groups. One experimental group received conventional treatment, whereas the other group received conventional treatment with pharmaceutical intervention for the treatment of vitamin D deficiency(vitamin D3 + calcium). Results: A significant reduction in periodontal inflammation was observed across all study groups starting from day 14 of treatment. However, in a longer perspective (12 and 18 months after treatment), the indices analyzed remained fairly stable and corresponded to the chronic periodontitis clinical stabilization stage in both groups. The conventional treatment group demonstrated a marked tendency for all indicators to return to the baseline. Conclusions: Pharmacotherapy of vitamin D deficiency contributed to the normalization of periodontal microcirculation (the σ and Kv values approached those of healthy periodontium) as evidenced by the immediate and long-term follow-up results. Clinical observation of patients suffering from moderate chronic generalized periodontitis with underlying hypovitaminosis D makes an argument to the use of vitamin D supplementation for the correction of vitamin D deficiency as a part of the complex treatment. Trial registration number: NCT67823273

Keywords: Periodontitis. Chronic generalized periodontitis. Hypovitaminosis D. Complex therapy.

Received: September 13, 2022
Revised: October 31, 2022
Accepted: November 10, 2022

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Introduction

Periodontal pathologies predominate in the morbidity profile of oral diseases and present one of the most challenging tasks for modern dentistry. Periodontal diseases are widespread among all age groups.[1,2] In Russia, periodontal diseases are detected in 98% of patients.[3] Chronic generalized periodontitis holds a special place among periodontal diseases.[4,5] According to the World Health Organization (WHO), up to 90% of the adult population living in developed countries present certain symptoms of chronic generalized periodontitis. These rates indicate inefficacy of the currently applied therapeutic and preventive measures.[6]

Many risk factors affect the pathogenesis of periodontal diseases, including poor oral hygiene, decreased saliva secretion, overhanging fillings, the presence of orthodontic appliances, dental and oral mucosal anomalies, mechanical damage, etc.[7]

Bacteria is the main etiological factor that triggers the development of inflammatory and destructive periodontal diseases. Microorganisms are able to penetrate through epithelial membranes, producing factors that can change or suppress the host's defense mechanisms, and cause bone resorption.[8]

Recently, close attention has been paid to the relationship between periodontal pathologies and systemic disorders that disrupt basic physiological functions, such as diabetes mellitus, impaired hormonal function of the reproductive system, cardiovascular and neurological diseases, rheumatism, metabolic disorders, hypovitaminosis, and others.[9-13] New data have been discovered regarding the mechanisms of development and the course of periodontal diseases in patients with functional hemodynamic disorders both at macro- and microlevels, endocrine pathologies, and deficiency diseases.[14] Systemic osteoporosis is considered one of the important factors that make a person predisposed to the development of generalized periodontitis, affecting the course of this disease.[15] Studies confirm a high pathogenetic relationship between inflammatory changes in the mucous membrane and changes in periodontal bone. These changes are likely to occur simultaneously.[16]

Currently, successful treatments of inflammatory periodontal diseases combine therapeutic, surgical, orthodontic, and orthopedic methods. To optimize the treatment process, new progressive methods that improve the quality of life of patients suffering from inflammatory periodontal diseases are introduced.[17]

The monitoring of calcium and vitamin D levels and the analysis of their impact on the development of chronic generalized periodontitis have received more attention in recent years. Studies show a clear relationship between periodontal health and vitamin D intake.[18,19] Vitamin D was supposed to be involved in bone metabolism and calcium-phosphorus homeostasis until recent times.[20] However, recent studies confirm that vitamin D coordinates bone metabolism, functions as an anti-inflammatory agent, and stimulates the production of antimicrobial peptides.[21] Vitamin D receptors, found among immune cells (T-cells, B-cells), play a vital role in calcium homeostasis. Vitamin D receptors activate killer cells and stimulate the phagocytic activity of macrophages. Previous research found that vitamin D gene activated by $1,25(OH)2D_3$ induces the expression of cyclic adenosine monophosphate (cAMP) and betta-defensin 4, which exhibits antimicrobial activity against pathogenic microorganisms.[22,23]

The worldwide problem of vitamin D deficiency, defined by serum 25(OH)D levels below 30 ng/mL, should be noted.[24,25] Confirmed by national studies involving different age groups, vitamin D deficiency is widespread in the Russian Federation.[26,27]

This study aims to evaluate the dynamics of clinical and laboratory indicators of the periodontal state and hemodynamics in patients receiving pharmaceutical intervention for the correction of vitamin D deficiency as a part of the complex therapy of chronic generalized periodontitis.

Methodology

Ethics approval and consent to participate

The research used was conducted according to the requirements of the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE). The study followed the ethical principles approved by the Human Experiments Ethics Committee of I.M. Sechenov First Moscow State Medical University (Protocol № 3 of 15.10.2019).

Study design

A randomized, open-label, prospective comparative clinical study was conducted in 2019-2020 at the

Dental Center, I.M. Sechenov First Moscow State Medical University (Russia). A total of 568 patients who were permanent resident of Moscow were examined. All of them were undergoing dental treatment at the Dental Center. Out of these, 148 patients met the inclusion criteria listed below. The sample size was calculated based on these 148 patients and met the following parameters: α=0.05; β (power)=0.95; effect size=0.5. According to calculations, the minimum sample size should be 107 patients.

Thus, out of the total number of patients examined who met the inclusion criteria, 110 patients were randomly selected to participate in the experiment.

The following inclusion criteria were applied to the experimental groups:

verified diagnosis according to ICD-10 – K05.3 chronic periodontitis;

moderate generalized periodontitis (3.5-5 mm periodontal pockets, less than 50% root resorption);

vitamin D deficiency (25(OH)<50 nmol/L);

young age (18-44 years old) according to WHO classification;

patient informed consent.

The exclusion criteria were as follows:

history of myocardial infarction, acute and chronic kidney diseases, use of anticonvulsants, and bowel and liver diseases;

pregnancy and lactation;

intolerance to vitamin D and calcium supplements;

patients who did not provide consent to participate in the study.

The method of simple randomization was applied to divide the study participants into the groups depending on the treatment prescribed to them. Group 1 included 55 patients who underwent conventional periodontal treatment without pharmaceutical intervention for the correction of vitamin D status. Group 2 consisted of 55 patients who underwent conventional periodontal treatment with pharmaceutical intervention for the correction of vitamin D status (vitamin D3 + calcium). The experimental groups consisted of 62 men and 48 women, whose average age was 31±9.3 years.

In addition, a control group (group 3) was formed, which included 40 patients with chronic generalized moderate periodontitis and normal vitamin D levels (25(OH)>50 nmol/L) who underwent conventional periodontal treatment. The sample size for the control group was calculated using the same parameters for the experimental groups. Control group inclusion and exclusion criteria were compliant with those established for the experimental groups. The age and gender distribution in the control group was similar to the pattern seen in the experimental groups.

The data were analyzed after all patients had undergone a full course of treatment. The study was open; masking and blinding were not used.

Clinical examination

During an initial appointment, the patients answered questions regarding their complaints, history of periodontitis, and history of other diseases. Clinical examination of the oral cavity included the assessment of oral mucosa, hard tissues of the teeth and gums, changes in the color of the mucous membrane of the oral cavity, the presence of bleeding gums, pathological tooth mobility, and supra- and subgingival calculus.

Clinical examination consisted of the following procedures:

Evaluation of the oral hygiene practices used by patients, following the Green-Vermilion index (oral hygiene index simplified, OHI-S).

Assessment of gingival bleeding intensity on probe using the Muhlemann index. Bleeding was measured on interdental papilla: score 1: a bleeding site at the tip of interdental papilla; score 2: bleeding along the line of contact of gingival papilla with hard tooth tissues; score 3: filling of interdental space with hemorrhagic exudate; and score 4: abundant bleeding from gingival papilla and gingival margins, with exudate filling 2-3 interdental regions.

Determination of the level of periodontal attachment loss (considers the depth of periodontal pocket and the level of gingival recession).

Calculation of the periodontal index. The periodontal state is evaluated for each tooth on the scale from 0 to 8. Periodontal index is defined as the sum of scores allocated to each tooth/number of teeth.

Evaluation of pathological tooth mobility according to the Miller's index modified by Fleszar.

Calculation of the papillary-marginal-alveolar index (pma) modified by Parma C.

Calculation of the Svrakoff iodine number. The gums are stained with the Schiller-Pisarev solution. The color of interdental papilla is given the score of 2; marginal gingiva: 4; alveolar gingiva: 8. Iodine number is defined as the sum of scores allocated to each tooth/number of teeth.

Laboratory tests

The blood content of the vitamin D marker, 25(OH), was evaluated. For the quantitative analysis of 25(OH), an enzyme immunoassay with a 25(OH)D ELISA kit (IDS, USA, Cat no. AC-57F1) was undertaken. The level of serum 25(OH)D was evaluated 12 months before and after periodontal treatment. Blood total calcium levels were measured to control the efficacy of the calcium metabolism therapy consisted of calcium and vitamin D supplements. The reference values were 2.15-2.55 mmol/L.

The capillary blood flow in the gingival mucosa was measured using laser Doppler flowmetry. To register blood flow in the gingival mucosa, a LAKK-OP laser capillary blood flow analyzer (LASMA, Russia) was used. The room temperature was about 24°C. The patients were allowed to rest during 15 minutes before the start of the diagnostic procedures. They were asked to refrain from smoking and taking foods or drinks that change microcirculation before the study procedures. Laser Doppler flowmetry was performed while the patients were sitting in the dental chair. A range of parameters were determined, such as the mean perfusion flow rate (M) per time interval; σ value, which is the average perfusion fluctuation relative to the mean blood flow M; and Kv value, which is the integral indicator of variations observed during the process. The values obtained during the control examination of 35 patients with healthy periodontium were considered the reference ones (M=20.07±0.5 conventional units, σ=3.08±0.12 conventional units, Kv=15.8±0.4%).

X-ray examination was performed using orthopantomograms, which are panoramic x-rays. The type of bone resorption, height, shape, and structure of the interalveolar septum, the state of furcations, and the signs of bone destruction were evaluated. The degree of resorption was assessed at the tips of the interdental septum based on the Fush index (IF) before and 18 months after the start of treatment.

Treatment methods

All patients underwent conventional local therapy and surgical treatment of periodontal pockets. They received professional oral hygiene, tips on dental care and monitoring for proper oral hygiene practice. The study participants also received local periodontal pockets therapy with a 0.2% solution of chlorhexidine digluconate, had metronidazole applied, and sanitation of the oral cavity.

An obligatory treatment stage of moderate chronic generalized periodontitis is surgery. Curettage of periodontal pockets, following the Znamensky-Junger-Sachs method, was used for single periodontal pockets with a depth of less than 5 mm in patients with no bone pockets and sufficient gums density. Curettage involved the following steps:

antiseptic treatment of the oral cavity and surgical operation plus local anesthesia;

removal of supragingival and subgingival calculus;

scraping of all walls of periodontal pockets, starting from the vestibular side, followed by the removal of granulations;

de-epithelialization of the outer pocket wall with the removal of epithelium from the walls and bottom of periodontal pockets;

root polishing for removing the remaining calculus and softened cement;

antiseptic treatment of the pocket and hemostasis;

tight pressing of the gum to the tooth and application of a dressing to protect the wound.

Two to six teeth were treated in each session. The interval between sessions was 2-3 days. Supportive care included professional oral hygiene, elimination of the risk factors, and functional selective grinding of the tooth surfaces.

Starting from the stage of preparation to dental surgery, group 2 patients were taking vitamin D3 at a dose of 800 IU per day and calcium at a dose of 500 mg per day. The duration of the prescribed therapy was 1 year. Those who were not taking vitamin D supplements were recommended to include vitamin D rich foods in their diet.

The efficacy of the complex therapy was evaluated 14 days, 3 months, 6 months, and 12 months after treatment. The long-term results were assessed 18 months after treatment.

Statistical methods

The study data obtained were processed by the method combining variational and statistical approaches with the use of the Statistica 6 package. The mean values (M) and the mean error (±m) were specified. The normality of data distribution was tested using the Shapiro-Wilk test. For normal distribution of data, independent two-sample Student's t-test was used to compare differences between the groups, and dependent paired Student's t-test was used to compare

intra-group values before and after treatment. For data with non-normal distributions, the Mann-Whitney test was used to compare differences between groups and the Wilcoxon test was used to compare intra-group values before and after treatment. Comparison of the experimental and control groups was performed using Student's test with Bonferroni correction.

The difference between the compared variables was considered significant at $p<0.05$. The Number needed to treat (NNT) calculation was used to assess the efficacy of the therapeutic measures arranged for the treatment of chronic generalized periodontitis in patients with vitamin D deficiency.

Results

In group 1 and group 2 patients, the pre-treatment serum 25(OH)D levels were 38.3±0.6 nmol/L and 38.7±0.9 nmol/L, respectively. Another analysis conducted 12 months later revealed a significant increase in serum 25(OH)D in patients taking vitamin D3 + calcium supplements (91.6±0.6 nmol/L). Meanwhile, the serum 25(OH)D content remained reduced (41.7±0.8 nmol/L) in patients receiving conventional treatment (Table 1).

After basic periodontal treatment provided by day 14, the Muhlemann bleeding index reduced by 3.6 times in the control group, by 2.6 times in group 1, and by 3.4 times in group 2. Thus, a significant difference between the pre-treatment and day 14 variables was observed in all study groups. However, there was no statistically significant intergroup difference confirmed by the Muhlemann index. The intergroup difference was not statistically significant after 3 months.

A significant difference between the Muhlemann index of group 1 and the other 2 groups was observed 6 months after treatment. After 12 and 18 months of observation, an increase in the index was seen in all groups. However, the changes were most evident in group 1, with the bleeding index approaching the baseline by month 18. The Muhlemann index growth rates were significantly lower in group 2 and 3 compared to group 1. After 18 months, the Muhlemann index remained fairly stable and corresponded to the chronic periodontitis clinical stabilization stage (Table 2).

The dynamics of periodontal index is presented in Table 3. As early as 14 days after the start of treatment, a significant reduction in the index value occurred in all study group as compared to the baseline. Subsequently, the periodontal index decreased in groups 2 and 3. A slower index reduction was seen by the month 6 of observation. However, the index values increased and approached the initial values after 18 months. After 6, 12, and 18 months, the divergence in the periodontal index of group 1 was significant.

Index values of pma, reflecting the presence and degree of periodontal inflammation, decreased significantly by day 14 of observation, which indicates the adequacy of the therapy received. A gradual and significant decrease in this parameter was traced throughout the entire observation period. It was a demonstration of the pronounced positive trend, seen

Table 1- The dynamics of serum 25(OH)D levels (nmol/L) in patients with chronic generalized periodontitis

Observation period	Group 1	Group 2	Group 3 (control)
Before treatment	38.3±0.6	38.7±0.9*	110.4±1.1*
After 12 months	41.7±0.8*	91.6±0.6*	113.7±1.2*

Note: *statistically significant intergroup difference, group 2 as compared to groups 1 and 3, $p<0.05$

Table 2- The dynamics of the Muhlemann index change in patients with different vitamin D status

Observation period	Group 1	Group 2	Group 3 (control)
Before treatment	2.6±0.05	2.7±0.07	2.5±0.06
After 14 days	1.0±0.06*	0.8±0.08*	0.7±0.07*
After 3 months	1.3±0.08*	1.1±0.07*	0.9±0.06*
After 6 months	1.7±0.08*, **	1.1±0.05*, **	1.1±0.06*, **
After 12 months	2.1±0.05**	1.2±0.04*, **	1.3±0.04*, **
After 18 months	2.2±0.1**	1.5±0.05*, **	1.4±0.05*, **

Note: *statistically significant difference as compared to the pre-treatment value, $p<0.05$; **statistically significant intergroup difference, $p<0.05$.

mainly in the control group and group 2. In group 1, an increase in the pma index was documented 6 months after the start of treatment. By month 18 of observation, the pma index exceeded those in the control group and group 2 by 2.2 and 1.8 times, respectively (Table 4).

The changes in the Svrakoff number are presented in Table 5. The Svrakoff index presented significant decrease compared to the pre-treatment values registered in all study groups on day 14 after the start of periodontal treatment. The control group had the index unchanged during the follow-up period. The experimental groups showed a trend towards a significant increase in this parameter during the observation period, which was more pronounced in group 1. Generally, the index values were significantly better in group 2 patients receiving pharmaceutical intervention for the correction of vitamin D status as compared to patients who did receive vitamin D3 supplements.

The dynamics of changes in the level of basal microvascular gingival blood flow, determined by laser Doppler flowmetry, is presented in Table 6. As evident, the average diagnostic parameters of the tissue blood flow were significantly worse in both experimental groups and control group than those in healthy individuals (the microcirculation index was increased, the 'flux' index and the coefficient of variation were lower), which indicated microcirculatory stagnation of the gums. After 6 months, some changes were observed in the periodontal tissues towards improving hemodynamics and tissue perfusion. This dynamic was least pronounced in group 1. In particular, the coefficient of variation increased by 12% in group 1, by 49% in group 2, and by 63% in group 3. The intergroup difference (group 1 as compared to groups 2 and 3) was statistically significant ($p<0.05$). In addition, a slight increase in the root-mean-square deviation (σ) was observed, which is typical for the tissue blood flow activation (less marked in group 1).

After 12 and 18 months of treatment, patients from groups 2 and 3 had the σ and Kv values approaching those measured in healthy patients. At the same time, these values remained unchangeably low in group 1 patients. The intergroup difference (group 1 as compared to groups 2 and 3) remained statistically significant ($p<0.05$). The X-ray examination performed 18 months after the start of treatment showed 0.02-0.03 units decrease in the resorption index (IF) in the control group and in patients receiving pharmaceutical intervention for the correction of hypovitaminosis D as compared to the data obtained before treatment. The patients who did not receive pharmaceutical intervention for the correction of vitamin D status had their resorption index (IF) decreased by 0.06 units. Thus, 18 months after the start of treatment, the

Table 3- The dynamics of the periodontal index change

Observation period	Group 1	Group 2	Group 3 (control)
Before treatment	5.4±0.06	5.4±0.08	5.3±0.07
After 14 days	5.0±0.04*	4.9±0.06*	4.8±0.04*
After 3 months	4.9±0.05*	4.6±0.04*	4.5±0.03*
After 6 months	4.7±0.03*, **	4.2±0.08*, **	4.1±0.1*, **
After 12 months	4.7±0.07*, **	3.7±0.1*, **	3.6±0.1*, **
After 18 months	5.1±0.07*, **	3.6±0.07*, **	3.3±0.06*, **

Note: *statistically significant difference as compared to the pre-treatment value, $p<0.05$; **statistically significant intergroup difference, $p<0.05$.

Table 4- The dynamics of the papillary-marginal-alveolar index (pma)

Observation period	Group 1	Group 2	Group 3 (control)
Before treatment	53.4±0.05	52.4±1.0	52.8±0.09
After 14 days	38.5±0.07*, **	32.4±0.06*, **	30.6±0.08*, **
After 3 months	29.8±0.1*, **	23.6±0.06*, **	22.3±0.03*, **
After 6 months	28.6±1.0*, **	22.9±0.1*, **	19.3±0.05*, **
After 12 months	32.6±1.1 *, **	21.8±0.09*, **	18.7±0.05*, **
After 18 months	36.3±0.06*, **	20.3±0.07*, **	16.4±0.08 *, **

Note: *statistically significant difference as compared to the pre-treatment value, $p<0.05$; **statistically significant intergroup difference, $p<0.05$.

intensity of bone resorption in patients taking vitamin D3 + calcium was lower than in patients who did not administer this supplement.

In most cases, complex therapy of chronic generalized periodontitis prolonged remission and reduced the number of relapses. However, the frequency of exacerbations varied between the groups. Thus, the average number of exacerbations registered over the entire observation period in patients who did not receive pharmaceutical intervention for the correction of hypovitaminosis D was 3.3±0.1 times a year. A relapse occurred 2.1±0.05 times a year. The remission periods were 2.6±0.1 months in patients who did not receive pharmaceutical intervention for the correction of hypovitaminosis D and 5.3±0.3 months in patients who received vitamin D supplements. Hence, regular use of vitamin D3 + calcium extended the remission period by an average of 2.7 months.

The analysis of the efficacy of the taken therapeutic measures showed that treatment of chronic generalized periodontitis with no pharmaceutical intervention for the correction of vitamin D status resulted in relapses of the disease in half of the study group patients. Meanwhile, only 12 relapses were documented among patients receiving pharmacotherapy of hypovitaminosis D.

Table 5- The dynamics of the Svrakov number

Observation period	Group 1	Group 2	Group 3 (control)
Before treatment	3.1±0.1	3.2±0.07	3.0±0.1
After 14 days	1.3±0.08*	1.1±0.06*	1.0±0.06*
After 3 months	1.4±0.1*, **	1.2±0.05*, **	0.8±0.05*, **
After 6 months	1.6±0.07*, **	1.3±0.08*, **	0.9±0.08*, **
After 12 months	1.8±0.06*, **	1.4±0.07*, **	0.9±0.04*, **
After 18 months	2.3±0.1*, **	1.6±0.06*, **	1.0±0.06*, **

Note: *statistically significant difference as compared to the pre-treatment value, p<0.05; **statistically significant intergroup difference, p<0.05.

Table 6- The dynamics of microcirculation changes during the treatment process

Observation period	M, (conventional units)	σ, (conventional units)	Kv (%)
Group 1 (conventional treatment, 25(OH)D<50 nmol/L)			
Before treatment	33.67±0.2	1.83±0.1	5.56±0.2
After 3 months	34.23±0.4	2.05±0.2	5.79±0.2
After 6 months	34.21±0.2*	2.12±0.1*	6.23±0.1*
After 12 months	31.34±0.2*	2.14±0.1*	6.42±0.1*
After 18 months	33.34±0.3*	2.18±0.3*	6.48±0.3*
Group 2 (conventional treatment + vitamin D3 + calcium, 25(OH)D<50 nmol/L)			
Before treatment	33.76±0.1	1.85±0.1	5.46±0.2
After 3 months	31.67±0.2*	2.07±0.2	6.34±0.2
After 6 months	30.23±0.3*	2.52±0.2*	8.12±0.3
After 12 months	30.91±0.2*	3.03±0.1*	9.74±0.1
After 18 months	30.22±0.2*	3.37±0.1*	11.34±0.1
Group 3 (control, conventional treatment, 25(OH)D>50 nmol/L)			
Before treatment	33.37±0.2	1.86±0.1	5.55±0.1
After 3 months	32.34±0.1	2.04±0.2	5.82±0.1
After 6 months	30.23±0.2	2.55±0.1	9.04±0.3
After 12 months	30.75±0.2	2.89±0.1	9.42±0.2*
After 18 months	30.89±0.2	3.32±0.1	11.17±0.1
Healthy periodontium, (n=35)			
Control examination	20.07±0.5	3.08±0.12	15.8±0.4

Note: *the changes in the comparison groups as compared to the control group are significant at p<0.01.

Discussion

Chronic generalized periodontitis can lead to early tooth loss. The disease affects masticatory performance, facial aesthetics, speech, and digestive and other body system functions. A close association between periodontal pathology and other diseases has been evidenced by high rates of other organ and system pathologies in patients with periodontitis.[10,19,28] Impaired microcirculation in periodontal tissues is of importance.[29,30] Several studies note that some patients may be genetically predisposed to the development of periodontal disease.[31] Besides, a relationship between stress and the severity of periodontitis has been confirmed.[32] Modern understanding of the etiology and pathogenesis of chronic generalized periodontitis considers systemic bone damage, which is called osteoporosis, of considerable concern.[33] Another fact worth mentioning is that the bone mineral content of the jaw is correlated with the severity of generalized periodontitis.[34]

Undoubtedly, the efficacy of the treatment received by patients with chronic generalized periodontitis depends on the involvement of factors influencing the pathological process. This justifies the in-depth approach to the diagnosis and treatment of periodontal disease.

Modern research has expanded the role of vitamin D in the regulation of multiple physiological processes in the body[35] It has been proven that vitamin D deficiency contributes to t.he development of not only skeletal, but also certain extraskeletal diseases.[36] The role of this vitamin in the development of dental pathologies and the most effective approaches to the diagnosis and treatment of periodontal disease is reassessed by a wide spectrum of biological effects of active vitamin D metabolites and a series of publications describing the relationship between the state of the oral cavity and vitamin D status.[18,19]

In order to increase the treatment efficacy of chronic generalized periodontitis in individuals suffering from vitamin D deficiency, this study investigates whether it makes sense to use conventional means and methods with the aid of pharmaceutical interventions for the correction of vitamin D deficiency as a part of the complex treatment of periodontal disease. Previous studies conducted in the Russian Federation collected data on the prevalence and profile of inflammatory periodontal diseases among patients with hypovitaminosis D.[24] A relationship between the degree of inflammatory and destructive processes in the periodontium and the status of vitamin D in the examined individuals has been found. According to this study, every third patient who applied for periodontal care was diagnosed with vitamin D insufficiency (as defined by the level of 25-OH<50 nmol/L). Among individuals suffering from inflammatory periodontal diseases and hypovitaminosis D, the majority of patients aged 33 to 36 years had mild (45.8%) or moderate chronic generalized periodontitis (44.4%). The frequency of inflammatory periodontal diseases was significantly increased in patients with vitamin D deficiency ($p<0.001$). The deviation of 25(OH)D level was detected only in 6% of patients with mild chronic generalized periodontitis and in more than 22% of patients with moderate and severe chronic generalized periodontitis. Considering the above, the assumption that a decrease in the serum level of vitamin D marker 25(OH) below 50 nmol/L is one of the risk factors contributing to the development of inflammatory periodontal diseases can be made.

We noted a significantly reduced periodontal inflammation by day 14 after the start of treatment, as evidenced by the positive dynamics of the Muhlemann index, periodontal index, pma, and Svrakoff number seen in all groups, although less pronounced in patients with vitamin D hypovitaminosis who did not undergo pharmaceutical intervention for the correction of vitamin D deficiency. However, in the long-term period (12 and 18 months after the start of treatment), the control group and patients undergoing pharmaceutical intervention for the correction of vitamin D status in the complex treatment of chronic generalized periodontitis had these values maintained at a fairly stable level, which corresponded to the chronic periodontitis clinical stabilization stage. The group where such correction did not occur demonstrated a marked tendency for all indicators to return to the pre-treatment levels.

According to the data obtained, pharmacotherapy of vitamin D deficiency in patients with chronic generalized periodontitis contributes to the normalization of microcirculation in the periodontium in the immediate and long-term follow-up. The pharmacotherapy presents a significant improvement in the integral index of capillary blood flow (with the σ and Kv values approaching those obtained for the healthy periodontium) and in the blood supply to periodontal tissues.

The use of pharmaceutical interventions for the correction of hypovitaminosis D as a part of the complex treatment of periodontal disease enabled reducing the number of relapses by 27% as compared to patients receiving conventional therapy. Moreover, the experimental strategy enabled maintaining a half longer remission as compared to the conventional therapy.

The limitations of this study are in the patients characteristics, as they were adult patients of young age with chronic generalized periodontitis of medium severity. Similar studies in children and elderly patients would also be of interest, as well as the use of medication correction of vitamin D deficiency as a prophylaxis for periodontal disease.

Conclusions

Clinical observation of patients with moderate chronic generalized periodontitis suffering from hypovitaminosis D justified the use of pharmaceutical interventions for the correction of hypovitaminosis D as a part of the complex treatment of periodontal disease. Significant changes in the index values reflecting the state and microcirculation of the periodontium in patients taking vitamin D3 + calcium indicate the effectiveness of the therapeutic measures arranged. The changes observed over time can be characterized as positive and stable. Regular intake of vitamin D3 + calcium allowed a 2.7 months longer remission compared to patients who did not use these supplements.

Thus, examination of patients with chronic generalized periodontitis, especially those having failed periodontal treatment, should involve a laboratory test of the serum level of 25(OH)D. Complex treatment of patients with chronic generalized periodontitis and underlying vitamin D deficiency should include a combination of vitamin D3 at a dose of at least 800 IU and calcium at a dose of 500 mg per day. To achieve a long-term and stable clinical effect, the course of pharmaceutical intervention for the correction of vitamin D deficiency should last at least 1 year (considering the climate typical for a particular region and dose adjustment in summer and winter).

Conflict of interest

The authors declared no conflicts of interest.

Data availability statement

The datasets used and/or analyzed in this study are available from the corresponding author on reasonable request.

Authors' contributions

Nesterova, Olga: Methodology (Equal); Formal analysis (Equal); Resources (Equal); Writing – review & editing (Equal). **Krasilnikova, Varvara:** Methodology (Equal); Resources (Equal); Supervision (Equal); Writing – original draft (Equal). **Margaryan, Edita**: Formal analysis (Equal); Resources (Equal); Supervision (Equal); Writing – original draft (Equal). **Lazareva, Yuliya:** Methodology (Equal); Resources (Equal); Writing – review & editing (Equal). **Nemtyreva, Liudmila:** Data curation (Equal); Formal analysis (Equal); Writing – original draft (Equal); Writing – review & editing (Equal).

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