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Bone Tissue Changes In The Background Of "Activation Of The Immune System" During Orthodontic Treatment And Tskaltubo Water Hormesis

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Abstract

The use of Tskaltubo radon-containing water in orthodontics will help to improve mineral metabolism, balance between osteoresorption and bone formation phases, and reduce the intensity of osteoclastogenesis. The use of Tskaltubo radon-containing mineral water in orthodontics in comparison with the traditional protocol treatment causes a statistically significant change in the reduction of activators of resorption processes in blood plasma, increase in the level of marker of new bone formation (acid-alkaline phosphatase), as well as osteochondrosis. In particular, a decrease in the sRANKL / OPG ratio and, consequently, a decrease in the level of osteoblastogenesis inhibitor produced by osteoclasts - sclerostin, which is produced by osteoclasts. All these processes already lead to the normalization of bone mineralization, which already has a positive effect on the processes of osteointegration, which other authors note even in the use of very small doses of radiation (hormesis). We have developed an algorithmic method for the diagnosis of patients with chronic generalized periodontitis and the rapid recovery of new bone tissue in

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the case of orthodontic treatment and the reduction of inflammatory processes over a long period of time.

Keywords: Radon Hormesis, Orthodontics, Osteoresorption, Osteoclastogenesis.

Introduction

During orthodontic treatment, periodontitis develops and bone tissue is damaged. Bone tissue is made up of cellular elements, an intercellular substance - the bone matrix and mineral components. The osteoblasts are called large basophilic cytoplasmic cells that have the ability to synthesize protein (they are the bone-forming cells); Osteoclasts - giant multicellular cells that break down bone tissue due to lysosomal enzymes; Osteocytes are metabolically inactive bone cells that attach to deep osteosynthetic cavities and form osteoblasts that are fixed in their own bone matrix. The cytokines secreted by mononuclear cells are chemical mediators that can interact directly or indirectly with bone cells. Cytokines, such as IL-1, can trigger the synthesis and secretion of many substances, including prostaglandins and various growth factors (Donaubauer A, 2020. Mendes E, 2019.)

The prostaglandins stimulate bone resorption and increase the speed of orthodontic tooth movement. Bone resorption lasts about 2 weeks, after which osteoclasts experience programmed cell death or apoptosis. After these processes, the preosteoblasts migrate into the resorption cavity and transform into osteoblasts. The fibroblasts also migrate along the cement line and secrete thin collagen fibrils around which osteoblasts begin to synthesize osteoids. Fibrils then enter the bone matrix and further mineralize to strengthen the new bone (Shemesh A, 2017).

The mineralization process begins and after about 4 months the resorption cavity is filled with new bone, in the stimulation of which Tskaltubo radon water will play an important role to further accelerate the bone formation process and activate the mineralization of osteoblasts. (Radon and image) As is known from the literature, radon is a radioactive gas and has an alpha radiation of 1 NK-37 Becquerel. It is a very small dose and therefore this effect is known as hormesis. Such hormesis effects cause the activation of nitric oxide (NO), which in turn leads to the formation of hydrogen peroxidase (H2O2); In the presence of H2O2, the production of excess NO in the microphages is stimulated by the action of interferon gamma and beta (INF-γβ) stimulates osteoblasts, in which the cytokines IL-1, IL-6, and TNF-α are involved (Kullmann M, 2019. Chikobava S, 2019). Formation of new osteoblasts and replacement of old bone tissue with new osteoblasts, because of which the space created by orthodontic treatment is filled with osteoblasts and consequently a newly formed bone (osteoid bone) is formed - the

mineralization of which is activated by Tskaltubo mineral water containing radon (Omiadze S, 2020 Nikolaishvili M, 2019).

This method is of practical importance because the orthodontic treatment requires intensive expensive medical services, treatment and, most importantly, time, because patients have an increased risk of developing inflammatory processes. Therefore, it is very important to create and refine all the new tools or methodologies that will ensure the safety of patients, help preserve their health, reduce the number of patients, the economic cost of the disease and alleviate the psychosocial burden on the patient and his relatives and health care system (Dondoladze Kh, 2021).

Therefore, the aim of the study was to facilitate orthodontic treatment in adolescent patients with mild to moderate periodontitis by inhalation of Tskaltubo water. To study changes in the concentration of cytokines (IL1, IL6 and TNF-α), humoral immunity (immunoglobulins: sIgA, IgA, IgG and IgM) and to evaluate the dynamics of clinical indicators, as both of these characteristics play a very important role in orthodontic treatment. The radon therapy enables us to study the speed and dynamics of changes in immunomodulation concentration (Dondoladze Kh, 2021).

Methodology. The treatment was performed in two groups of patients (75 people), clinical and laboratory examination with a diagnosis of moderate periodontitis. All patients underwent basic therapy equally. The first group received standard treatment, while the second group received radon therapy, which acts as an immunomodulator for the given treatment (Jiang YH, 2014 Kanungo M, 2013. Mendes E. 2019). To study the state of local immunity in the oral cavity, we studied the oral fluid of patients with anomalies of the jaw-tooth system. We used unstimulated mixed saliva as a material. Before taking the material, we offered the patient to rinse the mouth with boiled water at room temperature. None of the patients in the study had somatic disease, or pharmacotherapy was used. In all cases, we used sterile vials to take the material. The saliva was centrifuged at 3000 rpm for 15 minutes, after which it was frozen at -70 ° C.

The quantitative lysozyme content in the oral cavity was determined by immunoenzymatic analysis using Lysozym ELISA ("ImmunDiagnostik") test systems.

The "sIgA - IFA - BEST" kit was used to determine the quantitative content of sIgA or an immunoenzymatic solid-phase assay was applied.

The lysozym ELISA was also detected by IgA, IgG and IgM in venous blood by immunoenzymatic analysis. In order to assess its dynamics after wearing immune status and brace systems, we conducted cytokine content analysis, including: IL-1, IL-6, TNF-α, information on the cytokine content of patients in the main and study groups during brace fixation and their 3 months after wearing, presented in Tables 1 and 2.

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Research data and discussion

The patients were divided by sex, as we did not establish a statistically significant difference between the groups by sex ($p > 0.05$). Therefore, patients were divided into two groups, the first group treated with appropriate standard medications and the second group treated with radonized mineral water of Tskaltubo (baths and inhalations twice a day for 5-10 days).

Preliminary studies showed that the amount of sIgA in the dental tissue was not statistically different from the initial period, the reliability was observed only in 21 days of treatment in group 1, and in 10-14 days in the second group who were treated with only Tskaltubo radon-containing water. As it turns out, Tskaltubo radon-containing immunomodulatory treatment leads to a control sIgA control levels in the second group faster than in the first group, where the conservative 10treatment was administered. As can be seen from Table 1, there is a reliable difference between the groups by days and generally between the groups.

As for IgG and IgM in venous blood, there was a statistically significant difference in their levels. It should also be noted that the IgG level is 1.2 times higher than the norm (7 - 16 g / l), and the IgM level is 1.45 times higher than the norm (0.4 - 2.3 g / l).

Table 1. Dynamics of sIgA (g / l) in patients in saliva during treatment

Group	Observation time					
	Before treatment	7 days	14 days	21 days	30 days	3 months
1 group n = 36 Standard medical treatment	2,63±0,04	2,58±0,03	2,55±0,03	2,48±0,03 *	2,41±0,03 *	2,55±0,04
2 group n =33 Tskaltubo water (rinses and inhalation)	2,55±0,03	2,35±0,05	2,25±0,04 * **	2,15±0,03 * **	2,09±0,04 * **	2,10±0,01 * **

Note: * -Difference of credibility rates before treatment ** - Credibility rate compared to group 1

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Figure 1. Taking fluid from the tooth pocket

According to such an important factor of local immunity as sIgA, we can talk about the normalization of mucosal immunity in the 2nd group of patients undergoing orthodontic treatment when using Tskaltubo radon-containing water.

Table 2. Immunoglobulin IgA, IgG, IgM.

gr	Control Ind.	Observation time					
		Before treatment	7 days	14 days	21 days	30 days	3 days
1 gr	IgA (g/l) (0.7-4.0)	4,44±0,15	4,32±0,13	4,24±0,12	4,03±0,11	3,91±0,09	4,28±0,15
	IgG (g/l) (7-16)	20,2±0,36	19,5±0,38	18,3±0,29	18,0±0,28	17,2±0,26	19,4±0,42
	IgM (g/l) (0.4-2,3)	5,39±0,19	5,02±0,23	4,67±0,22	4,52±0,2	4,22±0,19	4,95±0,21
2 .	LgA (g/l)	4,47±0,15	4,11±0,1	3,80±0,11	3,44±0,12	3,00±0,09	2,72±0,09
	gG (g/l)	20,1±0,4	17,0±0,48	15,2±0,39	14,1±0,45	13,3±0,3	12,86±0,32
	IgM (g/l)	5,24±0,22	4,25±0,26	3,40±0,23	3,15±0,12	2,45±0,11	2,25±0,1

Note: * - Difference in belief rates before treatment ** - Credibility

On the 7th day of observation, all patients showed a tendency to decrease the concentration of antibodies, moreover, in the 2nd group, the decrease in the level of immunoglobulins (IgA, IgG, IgM) in venous blood differed significantly from the initial examination data ($p < 0.05$). The decreases in immunoglobulin levels in group 2 were associated with treatment with Tskaltubo radon-containing water (rinses and inhalation). These processes

helped to eliminate pathogenic factors of the periodontium (primarily of bacterial origin). The result was obtained in about 5-10 days), there was also a reduction in the development of antigenic processes and stress on the immune system, and at the same time the normalization of the level of humoral immunity. As for the first group, there were (traditional treatment of chronic generalized periodontitis - (stages of complex treatment with CGP scheme): professional oral hygiene, local drug therapy (antibacterial and anti-inflammatory), as well as the first and second groups began the surgical phase (Curettage of periodontal pockets, which lasted on average about 14-16 days). Comparing the first and second groups, it was found that the positive result of Tskaltubo radon water and the statistical difference between these two groups is not only in the reduction of the periodontal inflammatory process, but also in the change of treatment time. ($p < 0.05$). This fact proves that Tskaltubo water rinses and inhalations give results faster than traditional medical treatment. From the seventh day, there is a clear tendency in the antibody concentration decrease. The antibodies remained in both groups. Moreover, in group 2 sIgA venous blood had statistically significant differences compared to the first group. ($p < 0.05$) (see Table 1, Figure 1). There was a decrease in IgG and IgM levels in the venous blood of patients in group 1, while in group 2 all classes of immunoglobulins were statistically significantly reduced compared to group 1 ($p < 0.05$) (Chandra A, 2015. Choy M, 2020. Discacciati JA, 2020).

The IgA concentrations in the venous blood of all subjects corresponded to reliable values, although this rate was significantly lower in group 2 compared to the first, as well as IgG and IgM concentrations ($p < 0.05$) (Table 2). There are significant differences between the 1st and 2nd groups, which are observed with the involvement of the immunomodulatory effect of Tskaltubo radon-containing water, these data clearly reveal the harmonization of immunological reactivity, including humoral immunity factors (Bansal P, 2015. Deloch L 2018. Eftekhar L, 2017).

From the 14th day of the observation, the "advantage" of the 2nd group over the first became even more apparent and was statistically reliable. On the 21st and 30th days of treatment, similar trends were even more strongly observed in patients in both groups, both in the gingival fluid and in the venous blood, indicating a low concentration of immunoglobulins and at the same time being corespondent with control. sIgA, IgA, IgG levels and IgM in the 2nd group were statistically significantly lower than in the 1st group ($p < 0.05$). At the same time, IgA concentrations in both groups as well as IgG and IgM in group 2 correspond to reliable values. It should be noted that the decrease in immunoglobulin levels in group I is associated with traditional treatment of CPM (Chandra A, 2014. Deloch L, 2018. Donaubauer A, 2020). Traces have shown that there is a weakening of the inflammatory process and subsequent

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disappearance, but over a period of time there is a resumption of inflammatory events, an increase in antigen load and an increase in the concentration of antibodies. As for the 2nd group, the involvement of Tskaltubo water leads to the enhancement of the immunomodulatory effect, which is aimed at the harmonization of humoral immunity, which turned out to be much more important and was distinguished by a higher degree of maintenance of the obtained result.In our case, this new approach is the use of Tskaltubo radon-containing water for rinses and inhalation, which activates peripheral microcirculation and central hemodynamics. All of the above leads to the activation of the immune system. In particular, inhalation and rinses with Tskaltubo water cause activation of NO, which can be considered in the context of an autocrine homeostatic modulator. It has been established that macrophages-killers are an important source of NO; It is through NO activation that they inhibit the synthesis of tumor cell DNA and exert cell-suppressed, anti-inflammatory, desensitizing, and sedative action on tumor cells It regulates the ion exchange of Na, K and Ca, as shown in our previous experiments, inhibits specific autoimmune and activates the action of nonspecific immune systems. All of the above allows us to think that radon in Tskaltubo water causes a reduction of free radicals at the expense of activating the immune system, which in turn has a significant impact on the restoration of bone damaged by the use of orthodontic appliances, against the background of osteoblasts activation and, correspondingly, at the expense of the digestion of microorganisms developed in the periodontitis tissue.Therefore, we have studied the cytokines IL1, IL-6, (TNF-α - Tumor necrosis factor), tumor necrosis factor (TNF), as it is known from the literature (interferon (IFN)) have the most significant effect on bone tissue, affecting the differentiation of osteoblasts and bone resorption. IL-1, IL-3, IL-6, IL-11, TNF play an important role in the development of osteoclasts, which in turn leads to the regulation of local and systemic inflammatory reactions and participates in the alleviation of osteoporosis, IL-1 (produced by monocytes, macrophages, fibroblasts) enhances the differentiation of osteoclasts and therefore has a resorption effect (He F. 2019. Kanungo M, 2013).

The IL-6 is produced by activated monocytes or macrophages, endothelial cells, fibroblasts, activated T cells; stimulates the production of osteoblasts by producing glycoprotein receptors on stromal / osteoblastic cells, which in turn activates the kappa-β ligand of the receptor activator. At the same time, the discovery of this cytokine system RANKL-RANK-OPG contributed to an important understanding of the process of remodeling and pathogenesis of osteoporosis, and we can say that Tskaltubo radon-containing water can cause movement of the bones and the formation of free spaces (Discacciati JA, 2012. Deloch L, 2018,). RANKL is a glycoprotein produced

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by osteoclast cells and activated by T-lymphocytes, belonging to the tumor necrosis factor (Deloch L, 2018, Jiang YH, 2014).

Figure 2: The movement of the bones and the formation of free spaces

Is a superfamily of factor (TNF) ligands (Nikolaishvili M, 2019) and is a major stimulus for osteoclast maturation. The RANKL expressed on the surface of osteoblasts binds to the RANK receptor, which is located on the membranes of osteoclast progenitor cells and induces the process of osteoclast differentiation and activation. At the same time, osteoprotegerin (OPG) is a receptor for RANKL synthesized by osteoblast cells, as well as stromal cells, vascular endothelial cells, and B-lymphocytes, which act as RANKL endogenous receptors, interacting with their own endogenous receptor. Radon inhibits the formation of adult multinucleated osteoclast cells, disrupts the process of osteoclastogenesis and thus reduces bone resorption activity. IL-1 Ra (an IL-1 receptor antagonist), a natural inhibitor of IL-1β action, also plays a role in bone remodeling (Choy M,2020., Donaubauer A, 2020).

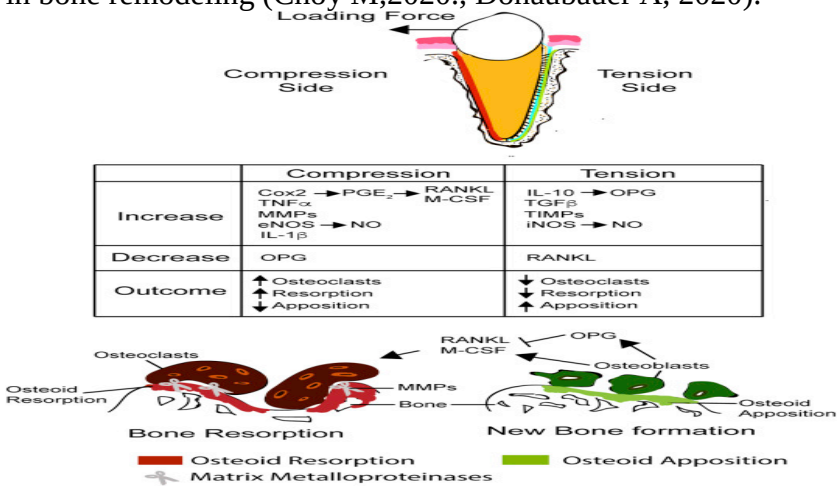

Figure 3: Regulation of osteoclasts and osteoblasts through Tskaltubo water

Thus, the imbalance between inflammatory (enhanced bone resorption) and anti-inflammatory cytokines (enhanced osteoblastogenesis) should be directed

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at increasing the content of cytokines involved in the inflammatory response, it is known that an increase in RANKL causes bone resorption. There is no doubt that this mechanism of bone remodeling disorder, which lies in the pathogenesis of osteoporosis, provides new opportunities for the search and treatment of modern methods in patients with impaired bone mineral density. In our case, it is Tskaltubo radon-containing water, which, according to our research, causes the regulation of these processes by the activation of osteoblasts during orthodontic treatment. Bone mineralization, RANKL-RANK-OPG modulation by cytokines IL-1β, IL-6 and TNF-α were studied in two groups we recruited (Chandra A, 2015. Deloch L, 2018. Eftekhar L, 2017). The 1-st group underwent conservative treatment, while the 2-nd group underwent water rinses and inhalation of Tskaltubo radon water for 5-10 days. It seems that radon-containing water in Tskaltubo causes a decrease in cytokine content in the 2-nd group and an approach to control, a further decrease in the case of TNF-α, all of which indicate rapid changes in inflammatory processes, which further enhance bone mineralization, positively affecting bone strength and the activation of osteoblasts (Choy M, 2020. Jiang YH, 2014).

Table 3: The role of cytokines in bone regeneration

Patient group	Cytokines	Gum tissue fluid	After 1 month	After 3 months
Control group	IL-1β IL-6 TNF- α	4.4 [3,9-5,8] 0,16 [0,11-0,18] 0,90 [0,68-1,06]	4.5 [4.1-5,7] 0,15 [0,12-0,17] 0,96 [0,78-1,05]	4.6 [4,0-5,6] 0,14 [0,11-0,16] 0,90 [0,77-1,04] P1<0,0001
Group 1 Standard medicinal Treatment	IL-1β IL-6 TNF- α	4.9 [4,2-5,6] 0.16 [0,14-0,18] 0.88 [0,73-1,04]	4.8 [3,9-5,4] 0.17 [0,15-0,20] 0.87 [0,74-1,09]	4.7 [4,0 -5,3] 0.16 [0,13-0,18] 0.86 [0,74-1,10] P1<0,0001
Group 2 Radon-containing water (inhalation and rinses) 5-10 days.	IL-1β IL-6 TNF- α	4.8 [4,0-5,6] 0.15 [0,13-0,18] 0.86 [0,73-1,04]	4.7 [3,9-5,4] 0.16 [0,15-0,20] 0.85 [0,74-1,09]	4.5 [4,0 -5,3] 0.15 [0,12-0,17] 0.87 [0,74-1,10] P1<0,0001

As it is known from the literature, the use of Tskaltubo radon-containing water causes a significant effect on bone tissue metabolism. All of this finds some expression in the modulation of the cytokine system and in the involvement of these processes which play a leading role in the RANKL-control mechanisms of bone tissue remodeling. RANK-OPG (Table 3). Receptor ligand solution form substitute - in kappa-B modulation of bone tissue nuclear factor. (sRANKL) activator in the control group was 0.139 [0.13-0.148] pmol / l, osteoprotegerin level - RANKL soluble (false) receptor that inhibits osteoclast formation and bone resorption - 3.66 [3.14-4.18] pmol / l, and sclerostin - an inhibitor of osteoblastogenesis - 225 [204-246] pmol / l.
Table 4 shows the content of some cytokines involved in osteoclastogenesis and osteoblastogenesis in the treatment of patients with chronic generalized periodontitis.

Table 4: Content of some cytokines in osteoclastogenesis and osteoblastogenesis

Indicator	Patient Group	Before treatment	After 1 month	After 2 months
sRANKL,pmol / l	Group 1, n=25	0,216 [0,195-0,237]	0,203 [0,182-0,225]	0,205 [0,200-0,231]
	Group 2, n=25	0,213 [0,193-0,231]	0,174 [0,157-0,185] P=0,0004	0,170 [0,155-0,178] P<0,0001 P1=0,0008
	Control Group		0.139[0.13-0.148]	
OPG,pmol / l	Group 1, n=25	4,67 [3,79-5,56]	4,26 [3,62-4,91]	4,54 [3,88-5,20]
	Group 2, n=25	4,21 [3,26-4,84]	4,01 [3,25-4,37]	4,32 [3,43-4,66]
	Control Group		3,66 [3,14-4,18]	
Sclerostin pmol / l	Group 1, n=25	284 [255-312]	280 [260-300]	288 [270-311]
	Group 2, n=25	288 [266-311]	232 [204-270] P=0,0063 P1=0,0234	228 [216-240] P=0,0388 P1=0,0013
	Control Group		225 [204-246]	

Discussion

Based on each of the above, it can be said that the use as a rinses and inhalation of Tskaltubo water leads to improved bone mineralization, reduced osteo-resorption intensity, increased intensity in the bone formation phases and decreased osteoclastogenesis. Tskaltubo radon-containing water causes enhancement of Ca, K, Na metabolism, which in itself has a positive effect on the statistically significant reduction of the inflammatory process and inflammatory markers in periodontal tissue and the enhancement of bone mineralization of bone tissue and the use of Tskaltubo radon-containing water

at the expense of activating the vascular system. (Donaubauer,A, 2020. Eftekhar L, 2017. Mendes E, 2019. Chikobava S, 2019)

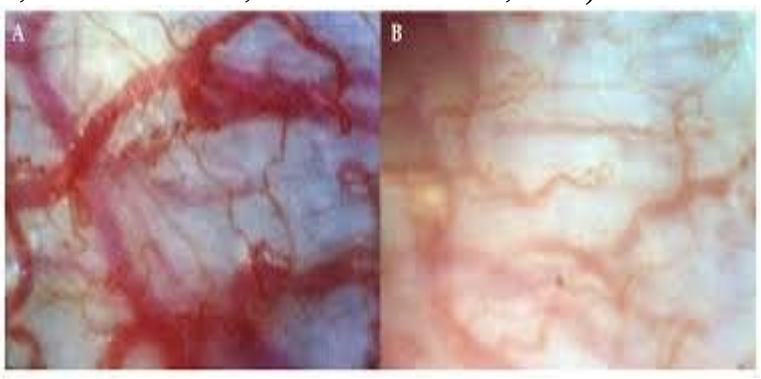

Fig. 4: Mineralization of bone tissue and the use of Tskaltubo radon-containing water at the expense of activating the vascular system**.**

While in plasma it causes a decrease in the content of resorptive markers, also acts on the regulation of osteoclastogenes in blood plasma - sRANKL and activation of osteoprotogrin by reducing the osteoblastogenesis inhibitor namely sclerostin produced by osteoclasts. β-RPA (inhibitor of resorption processes) causes changes in the regulators of osteoclastogenesis (Nikolaishvili M, 2019. Vasconcelos KF, 2016. Wrigh L, 2015).

Thus it can be said that the use of Tskaltubo radon-containing water in orthodontics will help to improve mineral metabolism, balance between osteoresorption and bone formation phases, and reduce the intensity of osteoclastogenesis. The use of Tskaltubo radon-containing mineral water in orthodontics in comparison with traditional protocol treatment leads to a statistically significant change in the reduction of activators of resorption processes in blood plasma, an increase in the level of AAP (acid-alkaline phosphatase) marker of new bone tissue formation. As well as changes in osteoclatogenesis - regulation of sRANKL and osteoprotegerin, in particular a decrease in the sRANKL / OPG ratio and consequently a decrease in the level of osteoblastogenesis inhibitor - sclerostin produced by osteoclasts, which is produced by osteoclasts (Omiadze S,2020. Shemesh A, 2017. Rogers S, 2020).

All of these processes already lead to the normalization of bone mineralization, which already has a positive effect on the processes of osteointegration, which other authors note even in the case of the use of very small doses of radiation (hormesis). We have developed an algorithmicmethod for the diagnosis of patients with chronic generalized periodontitis and the rapid recovery of new bone tissue in the case of orthodontic treatment and the reduction of inflammatory processes over a long period of time.

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