UDC 616.314.17-008.1:616.71-007.234-08 https://doi.org/10.26641/2307-0404.2022.4.271221

K.E. Pechkovskyi [1] [*], ***M.M. Kolotilov*** [1], ***I.M. Pechkovska*** [2], ***T.O. Timokhina*** [1]

SYSTEMIC CORRECTION OF OSTEOPOROSIS OF THE ALVEOLAR PROCESSES OF THE JAW IN COMPLEX TREATMENT OF PATIENTS WITH GENERALIZED PERIODONTITIS

Bogomolets National Medical University [1]
Taras Shevchenko boul., 13, Kyiv, 01601, Ukraine
[*]*e-mail: konpech.work@gmail.com*
PHEI «Kyiv Medical University» [2]
Boryspilska str., 2, Kyiv, 02093, Ukraine
e-mail: info@kmu.edu.ua
Національний медичний університет імені О.О. Богомольця [1]
бул. Тараса Шевченка, 13, Київ, 01601, Україна
ПВНЗ «Київський медичний університет» [2]
вул. Бориспільська, 2, Київ, 02093, Україна

Цитування: Медичні перспективи. 2022. Т. 27, № 4. С. 185-191
Cited: Medicni perspektivi. 2022;27(4):185-191

Key words: *generalized periodontitis, melatonin, vitamin D, alveolar process*
Ключові слова: *генералізований пародонтит, мелатонін, вітамін Д, альвеолярний відросток*

Abstract. Systemic correction of osteoporosis of the alveolar processes of the jaw in complex treatment of patients with generalized periodontitis. Pechkovskyi K.E., Kolotilov M.M., Pechkovska I.M., Timokhina T.O. *Generalized periodontitis is accompanied by progressive bone atrophy of the alveolar process of the jaws. The first signs of osteoporosis appear in the alveolar process already in the early stages. Complex treatment of generalized periodontitis includes, first of all, an etiopathogenetic approach. The object of the study is to investigate the effectiveness of biotherapeutic correction of osteoporosis of the alveolar processes of the jaws in the complex treatment of patients with generalized periodontitis adding melatonin and vitamin D. The study involved 121 patients aged from 26-40 years with generalized periodontitis of initial-I and I stages with a chronic course, and 45 apparently healthy volunteers from the control group. All patients gave voluntary informed consent to participate in the study. Groups of patients were randomized approximately by same age and gender. Before onset of treatment and 6 months after the complex treatment the level of vitamin D and melatonin level was measured and examined for osteoporosis using a cone-beam computed tomography. In order to give a qualitative and quantitative assessment of the state of mineralization of the spongy and compact bone tissue of the alveolar processes of the jaws histographic analysis of computed tomography was used. 55 patients in addition to traditional local treatment were added vitamin D intake of 4000 IU/d with meals and melatonin intake of 1.5 mg at bedtime for 1 month. It was stated, that level of melatonin in saliva is inversely proportional to the level of vitamin D in the blood serum in patients with generalized periodontitis and patients from the group with clinically healthy periodontium. Using melatonin and vitamin D in the complex of treatment of patients with generalized periodontitis leads to an increase X-ray density of bone tissue of the alveolar processes of the jaws, which allows to achieve restoration of bone density of alveolar processes and longer stabilization of dystrophic – inflammatory process in the periodontium. To strengthen the bone tissue of the alveolar processes of the jaws in patients with generalized periodontitis, it is advisable to use melatonin and vitamin D in a complex treatment.*

Реферат. Системна корекція остеопорозу альвеолярних відростків щелеп у комплексному лікуванні хворих на генералізований пародонтит. Печковський К.Є., Колотілов М.М., Печковська І.М., Тімохіна Т.О. *Генералізований пародонтит супроводжується прогресуючою атрофією кістки альвеолярного відростка щелеп. Уже на ранніх стадіях захворювання в альвеолярному відростку виникають вогнища остеопорозу. Комплексне лікування генералізованого пародонтиту включає в першу чергу етіо-патогенетичний підхід. Мета роботи: дослідити ефективність біотерапевтичної корекції остеопорозу альвеолярних відростків щелеп у комплексному лікуванні хворих на генералізований пародонтит з використанням мелатоніну й вітаміну Д. У дослідженні брав участь 121 хворий на генералізований пародонтит початкового-I та I ступенів з хронічним перебігом, віком 26-40 років, та 45 умовно здорових волонтерів контрольної групи, які дали поінформовану згоду на дослідження. Розподіл хворих у групах за віком і статтю був приблизно однаковим. До початку лікування та через 6 місяців після комплексного лікування вимірювали вміст вітаміну Д у сироватці крові та мелатоніну в слині, проводили обстеження на остеопороз за допомогою конусно-променевого комп'ютерного томографа.*

Для якісної і кількісної оцінки стану мінералізації губчастої і компактної кісткової тканини альвеолярних відростків щелеп використовували гістографічний аналіз комп'ютерно-томографічних зображень. 55 пацієнтам застосовували додатково до традиційного місцевого лікування вітамін Д по 4000 МО під час їди та мелатонін по 1,5 мг перед сном протягом 1 місяця. Установлено, що вміст мелатоніну в слині зворотно пропорційний вмісту вітаміну Д в сироватці крові у хворих на генералізований пародонтит й осіб у групі з клінічно здоровим пародонтом. Використання мелатоніну й вітаміну Д у комплексному лікуванні хворих на генералізований пародонтит приводить до підвищення у них рентгенівської щільності кісткової тканини альвеолярних відростків щелеп, що дозволяє досягти більш тривалої стабілізації дистрофічно – запального процесу в пародонті. Для зміцнення кісткової тканини альвеолярних відростків щелеп у хворих на генералізований пародонтит доцільно в комплексному лікуванні використовувати мелатонін і вітамін Д.

Generalized periodontitis (GP) is accompanied by progressive bone atrophy of the alveolar process of the jaws. The first signs of osteoporosis appear in the alveolar process already in the early stages. Complex treatment of generalized periodontitis includes, first of all, an etiopathogenetic approach. Therefore, to achieve an earlier and long-term stabilization of the dystrophic-inflammatory process in the periodontium we proposed an algorithm for the complex treatment of generalized periodontitis, which includes besides local GP treatment (phase I) [5] also a systemic use of biotherapeutic drugs: melatonin (MLT) and vitamin D (VD) [2, 8, 10].

MLT is the main pineal gland hormone, an endogenous integrator, chronomodulator and regulator of the body's circadian rhythms. It also provides osteogenic differentiation of mesenchymal stem cells, the formation and protection of bones; modulates the activity of osteoblasts and osteoclasts; reduces pain sensitivity [12, 15]; affects the intracellular calcium content, depending on the dose it has anti-stress, sedative, immunostimulating, cytoprotective, antimicrobial and anti-inflammatory effects [4, 14, 15]. In the oral cavity MLT is synthesized by salivary glands and gum tissues [3, 8].

VD is a necessary participant in the process of normal bone remodeling [7], that in addition, produces antibacterial, anti-inflammatory (anticytokine), immunomodulatory, normoglycemic, antidepressant, antiproliferative, analgesic, anabolic, lipolytic, organoprotective, hypotensive effects, regulates apoptosis, angioneogenesis [2, 7].

The object of the study is to investigate the effectiveness of biotherapeutic correction of osteoporosis of the alveolar processes of the jaws in the complex treatment in patients with generalized periodontitis adding melatonin and vitamin D.

MATERIALS AND METHODS OF RESEARCH

The study involved 121 patients with GP of initial-I and I stages aged from 26-40 years with a chronic course and 45 apparently healthy volunteers from the control group. Groups of patients were randomized approximately by same age and gender.

All patients from the main and two control groups in were included the study after obtained informed consent to undergo the planned clinical, radiological, laboratory and therapeutic measures. The research was conducted in accordance with the principles of bioethics set out in the WMA Declaration of Helsinki – "Ethical principles for medical research involving human subjects" and "Universal Declaration on Bioethics and Human Rights" (UNESCO).

Selection criteria for the control group: the presence of clinically healthy gums without any signs of bleeding during probing, the absence or insignificant amount of dental plaque, the absence of periodontal pockets with depth of >3 mm [3].

Selection criteria for patients together with chronic course of generalized periodontitis: the presence of local traumatic factors (plaque and calculus) in an insignificant or moderate amount, generalized bleeding during probing and loss of the attachment level more than in 30% of periodontal areas with radiological verification of bone loss in alveolar process.

Exclusion criteria from the study for patients of all groups: the presence of comorbid diseases and bad habits (smoking, alcoholism), the use of chewing gum, refusal of the study.

Generalized periodontitis in patients was diagnosed on the basis of a protocol that included the following criteria: the presence of at least 20 teeth in the mouth; at least 40% of periodontal areas with a depth of probing periodontal pockets ≤4 mm and loss of the level of attachment from 0 to 4 mm; more than 40% of areas with bleeding during diagnostic probing; not less than 2 sextants with radiographically confirmed loss of the height of the alveolar bone (interdental septa) from 0 to 4 mm [10].

Local treatment. All 45 practically healthy volunteers and 121 patients with GP of initial-I and I stage underwent clinical and radiological and laboratory examinations, training in rational oral hygiene or its correction. All study participants received total professional oral hygiene. Supergingival dental deposits were identified and removed, and the surfaces of tooth crowns were polished. Then, dental deposits (biofilm and tartar) were removed from the surfaces of the roots of the teeth under the gums, detoxification

and polishing of the roots. In patients with GP epithelium of pockets and infiltrated adjacent connective tissue was removed from (subgingival curettage).

From the beginning of treatment (within 6 visits) to all patients with GP anti-inflammatory and antimicrobial dressings based on mefenate ointment, with added antimicrobial drugs depending on the composition of the microflora of the periodontal pockets were applied into periodontal pockets and gums. If the cocci microflora prevailed, furazolidone was added, in the presence of a significant number of fungi – nystatin, in the presence of protozoa or the predominance of fuso-spiral symbiosis – metronidazole. At home – oral baths with 0.12% chlorhexidine solution after teeth brushing 2 times a day for 1 minute within 7 days.

After the disappearance or significant reduction of signs of gingival inflammation (hyperemia, swelling, bleeding), 55 patients were *additionally treated* with VD (4000 IU/d) and MLT (1.5 mg), which lasted for 1 month. To study the effect of these drugs on the density of bone tissue in patients with GP before and 6 months after the complex treatment the level of VD and MLT level, was measured and examined for osteoporosis using a cone-beam computed tomography. In order to give a qualitative and quantitative assessment of the state of mineralization of the spongy and compact bone tissue of the alveolar processes of the jaws histographic analysis of computed tomography was used [16]. It is known that an increase / decrease in X-ray density reflects the strengthening / weakening of bone structures [16].

Samples (0.5 ml of unstimulated solid saliva and 2 ml of peripheral blood) were collected from 9:00 to 11:00 under standard lighting before starting treatment and 6 months after treatment. Patients refrained from eating, drinking (water only), smoking, chewing gum, teeth brushing, and using mouthwash from the evening until the time of sampling in order to exclude any possible obstacles.

Saliva samples were collected using cotton swabs (Salivette, Sarstedt, Nümbrecht, Germany). The level of MLT in saliva was determined using an ELISA kit (ELISA without melatonin withdrawal from saliva, IBL, Hamburg, Germany) according to the manufacturer's instructions. The assay method has an analytical sensitivity of 0.3 pg/ml, a functional sensitivity of 0.3 pg/ml, a coefficient of variation within the assay of 6.1%, and a coefficient of variation between analyzes of 7.6% in the range of expected values.

Level of vitamin 25 (OH) D (25-hydroxycalciferol) in blood serum was determined by the immunochemiluminescent method on an automatic analyzer ARCHITECT 25-OH Vitamin D Controls. The detection limit were 2.1 ng/ml, the coefficient of variation within the assay – 5.2%, the coefficient of variation between analyzes – less than 7%.

Patient stratification (except for the study design) was carried out according to the classification of the VD level according to Horas: deficiency – <20 ng/ml; suboptimal level – 20-30 ng/ml; optimal level (target status) – 30-50 ng/ml; high content – 50-100 ng/ml; dangerous level – > 100 ng/ml.

In accordance with the stratification by the level of VD there were the following groups: examined patients only: 1 (optimal level), 2 (suboptimal level) and 3 (deficit); control groups of conditionally healthy volunteers; examined and treated according to the traditional protocol: K4 (optimal level), K5 (suboptimal level), K6 (deficit) and K7 (optimal level), K8 (suboptimal level), K9 (deficit) groups of patients with GP, accordingly; examined and treated with biotherapeutic correction: 4 (optimal level), 5 (suboptimal level), 6 (deficit) and 7 (optimal level), 8 (suboptimal level), 9 (deficit) groups of patients with GP. To 55 patients from 4, 5, and 6 groups in addition VD intake of 4000 IU/d with meals and MLT intake of 1.5 mg at bedtime for 1 month was administered.

Statistical data processing was carried out by methods of variation statistics using the Microsoft Excel 2010 (License 02260-018-0000106-48794) and Statistica 6.1 (Serial number AGAR909E415822FA) with the definition of the arithmetic mean (M), mean error (m), Student's t-distribution [1].

RESULTS AND DISCUSSION

According to measurements of VD level, stratification of patients and patients of the control group there were made 9 groups. The reliability of stratification/structuring of groups according to the content of VD were performed within the triads. Comparison of the effectiveness of treatment was carried out only between groups with the same level of VD. The examination results of patients by groups are presented in Tables 1 and 2.

The level of VD in patients before treatment was at the lower level of the optimal, suboptimal and insufficient ranges and significantly lower than the corresponding ranges of almost healthy individuals of 1, 2, 3 groups ($p<0.01$). Changes in the level of VD in patients from k7, k8, k9 groups after traditional treatment are statistically insignificant ($p>0.01$) in comparison with initial values before treatment. At the same time, the level of VD in patients of 7, 8, 9 groups after treatment with biotherapeutic correction significantly increased ($p<0.01$).

Table 1

Level of vitamin D in blood serum and melatonin level in oral fluid (M±m)

Groups		VD, ng/ml	P	MLT pg/ml	p
No. tem	n				
Control: conditionally healthy volunteers					
1	11	38.1±0.9	–	2.23±0.21	–
2	14	26.3±1.1	$p_{12}<0.01$	2.95±0.24	$p_{12}>0.01$
3	20	17.1±0.9	$p_{13}<0.01$; $p_{23}<0.01$	4.05±0.36	$p_{13}<0.004$; $p_{23}>0.07$
Patients before treatment					
к4	22	33.1±1.2	$p_{1к4}<0.01$	6.29±0.39	$p_{1к4}<0.011$
к5	22	24.6±1.1	$p_{2к5}<0.009$; $p_{к4к5}<0.008$	8.51±0.57	$p_{2к5}<0.012$; $p_{к4к5}>0.08$
к6	22	13.7±1.1	$p_{3к6}<0.007$; $p_{к4к6}<0.009$; $p_{к5к6}<0.01$	12.15±0.71	$p_{3к6}<0.009$; $p_{к5к6}>0.07$
After traditional treatment					
к7	21	34.0±1.2	$p_{к4к7}>0.09$	5.99±0.35	$p_{к4к7}>0.07$
к8	21	25.3±1.2	$p_{к5к8}>0.07$	8.06±0.48	$p_{к5к8}>0.08$
к9	19	14.5±1.2	$p_{к6к9}>0.08$	11.24±0.58	$p_{к6к9}>0.09$
Patients before treatment					
4	16	33.5±1.1	$p_{14}<0.01$	6.36±0.43	$p_{14}<0.011$
5	18	23.9±1.2	$p_{25}<0.009$; $p_{45}<0.008$	8.98±0.65	$p_{25}<0.012$; $p_{45}>0.08$
6	21	12.3±1.1	$p_{36}<0.007$; $p_{46}<0.009$; $p_{56}<0.01$	12.25±0.64	$p_{36}<0.009$; $p_{56}>0.07$
After treatment with biotherapeutic correction					
7	16	37.8±1.1	$p_{47}<0.009$	5.73±0.37	$p_{47}>0.07$
8	18	27.7±0.9	$p_{58}<0.007$	8.14±0.52	$p_{58}>0.06$
9	21	16.3±1.2	$p_{69}<0.008$	9.47±0.61	$p_{69}<0.008$

Notes: M – arithmetic mean; m – mean error; p – level of significance; k – control group of patients.

The level of MLT in patients before treatment was higher than the corresponding rate of almost healthy individuals ($p<0.01$). If after traditional treatment in patients of k7, k8, k9 groups the level of MLT decreased by 4.8%, 5.3% and 7.5%, accordingly, and had unreliable character ($p>0.01$), in patients of 7, 8, 9 groups after treatment with biotherapeutic correction a significant decrease in the indicator by 9.9%, 9.3% and 22.7%, accordingly was noted.

Table 2

X-ray density (Hounsfield unites) of bone structures of alveolar processes

Group	Bone tissue	M±m	p
Control: conditionally healthy volunteers			
1	**Compact**	**1855±89**	**–**
	Spongy	**681±15**	**–**
2	**Compact**	**1605±78**	**$p_{12}>0.07$;**
	Spongy	**539±12**	**$p_{12}<0.008$**
3	**Compact**	**1471±63**	**$p_{13}>0.09$; $p_{23}>0.08$**
	Spongy	**480±11**	**$p_{13}<0.008$; $p_{23}<0.01$**
Patients before treatment			
к4	**Compact**	**1339±73**	**$p_{1к4}<0.008$**
	Spongy	**520±11**	**$p_{1к4}<0.007$**
к5	**Compact**	**1195±61**	**$p_{2к5}<0.009$; $p_{к4к5}>0.09$**
	Spongy	**437±12**	**$p_{2к5}<0.008$; $p_{к4к5}<0.01$**
к6	**Compact**	**1043±62**	**$p_{3к6}<0.008$; $p_{к4к6}>0.07$; $p_{к5к6}>0.09$**
	Spongy	**344±11**	**$p_{к3к6}<0.01$; $p_{к4к6}<0.01$; $p_{к5к6}<0.09$**
After traditional treatment			
к7	**Compact**	**1385±78**	**$p_{к4к7}>0.09$**
	Spongy	**531±13**	**$p_{к4к7}>0.24$**
к8	**Compact**	**1251±69**	**$p_{к5к8}>0.29$**
	Spongy	**465±15**	**$p_{к5к8}>0.28$**
к9	**Compact**	**1219±71**	**$p_{к6к9}>0.33$**
	Spongy	**375±15**	**$p_{к6к9}>0.69$**
Patients before treatment			
4	**Compact**	**1345±58**	**$p_{14}<0.008$**
	Spongy	**493±10**	**$p_{14}<0.007$**
5	**Compact**	**1191±53**	**$p_{25}<0.009$; $p_{45}>0.09$**
	Spongy	**408±11**	**$p_{25}<0.008$; $p_{45}<0.01$**
6	**Compact**	**1022±53**	**$p_{36}<0.008$; $p_{46}>0.07$; $p_{56}>0.09$**
	Spongy	**332±10**	**$p_{36}<0.01$; $p_{46}<0.01$; $p_{56}<0.09$**
After treatment with biotherapeutic correction			
7	**Compact**	**1486±48**	**$p_{47}>0.09$**
	Spongy	**605±14**	**$p_{47}<0.009$**
8	**Compact**	**1308±51**	**$p_{58}>0.07$**
	Spongy	**568±16**	**$p_{58}<0.008$**
9	**Compact**	**1184±53**	**$p_{69}>0.01$**
	Spongy	**421±17**	**$p_{69}<0.009$**

Notes: M – arithmetic mean; m – mean error; p – level of significance; k – control group of patients.

The X-ray density (XR D) of the bone structures was much lower than the analogous indicator of practically healthy individuals from 1, 2, 3 groups ($p<0.01$). 6 months after traditional treatment no significant changes in the indicator were detected, and after treatment with biotherapeutic correction significant increase in the indicator for spongy bone ($p<0.01$) was determined. In the aspect of comparing the results with the data of other researchers we obtained the following results for the control group: we noted that in saliva samples the level of MLT values varied from 0.07 pg/ml to 22.9 pg/ml [3, 11, 13], median MLT values in one study – in the range from 27.22 pg/ml to 103.93 pg/ml [9], MLT of gingival fluid – from 0.06 to 18.8 pg/ml [6], gum tissue – from 0.54 up to 1.58 pg/ml [3, 4]. The level of MLT in saliva, according to our study, increases with the severity of periodontitis, which generally corresponds to the data [12, 15]: the indicator in the control group varied from 0.80 pg/ml to 6.80 pg/ml with an average value of 3.92±0.58 pg/ml, from 3.30 pg/ml to 10.90 pg/ml, on average 6.87±0.82 pg/ml in the gingivitis group and from 5.20 pg/ml to 14.80 pg/ml with an average value of 10.20±0.98 pg/ml in the periodontitis group. The increase in the level of MLT in saliva in generalized periodontitis is inversely proportional to the level of VD in the blood serum, which is possibly justified by the design of our study and the stratification of patients by the level of VD. According to research [6], VD is rather an associative than a causative factor of acute and chronic diseases. Only on a computed tomographic image of the alveolar process of the jaws it is possible to identify spongy and compact tissues and measure the X-ray density (RD) to quantify their strengthening during treatment. The informativeness of this approach is shown in the study [16]. Dual-energy X-ray osteodensitometry allows only indirect assessment of changes in the alveolar process by measuring mineral density in the femur. Ultrasonic osteodensitometry does not have the ability to differentiate the spongy and compact tissues of the alveolar process of the jaws.

It was found that the X-ray density of the compact bone of the alveolar processes of patients in groups 4, 5, 6 is less than the corresponding indicator of relatively healthy individuals from 1,2 and 3 groups by 27.5%, 25.8% and 30.5% ($p<0.01$), accordingly; X-ray density of spongy bone – by 27.6%, 24.3% and 29.9% ($p<0.01$), accordingly. X-ray density of compact bone of alveolar processes of patients from 7, 8, 9 groups in 6 months after treatment increased by 10,5%, 9,8% and 15,9% in comparison with patients from 4, 5 and 6 groups ($p<0,01$) accordingly; The X-ray density of spongy bone increased by 2.4% ($p>0.06$), 14.7% and 17.2% ($p<0.01$) respectively. The ratio of X-ray density of compact bone and X-ray density of spongy bone was in the range from 2.72 (1 group) to 3.01 (3 group), from 2.72 (4 group) to 2.99 (6 group), from 2.79 (group 8) to 2.95 (group 9), which may indicate a certain constant that reflects the processes of bone remodeling. The X-ray bone density of alveolar processes in patients increased after treatment: compact bone by an average of 12.1%, spongy bone – by 11.4% ($p<0.01$), which indicated the effectiveness of biotherapeutic correction.

CONCLUSIONS

1. The level of melatonin in saliva is inversely proportional to the level of vitamin D in the blood serum in patients with generalized periodontitis and patients from the group with clinically healthy periodontium.
2. Using melatonin and vitamin D in the complex of treatment of patients with generalized periodontitis leads to an increase of X-ray density of bone tissue of the alveolar processes of the jaws, which allows to achieve restoration of bone density of alveolar processes and longer stabilization of dystrophic – inflammatory process in the periodontium.
3. To strengthen the bone tissue of the alveolar processes of the jaws in patients with generalized periodontitis, it is advisable to use melatonin (1.5 mg) and VD (4000 IU/d) in the complex treatment.

Contributors:

Pechkovsky K.E.– administration, research, writing;

Kolotilov M.M. – conceptualization, methodology, software;

Pechkovskaya I.M.– investigation, writing – review & editing;

Timokhina T.O. – investigation, writing – original draft.

Funding. This research received no external funding.

Conflict of interests. The authors declare no conflict of interest.

REFERENCES

1. Antomonov MYu. [Mathematical processing and analysis of biomedical data]. Kyiv: Medynform; 2018. ISBN 978-966-409-202-6.

2. Amrein K, Scherkl M, Hoffmann M. Vitamin D deficiency 2.0: an update on the current status worldwide. Eur J Clin Nutr. 2020;74:1498-513. doi: https://doi.org/10.1038/s41430-020-0558-y

3. Balaji TM, Vasanthi HR, Rao SR. Gingival, Plasma and Salivary Levels of Melatonin in Periodontally Healthy Individuals and Chronic Periodontitis Patients: A Pilot Study. Journal of Clinical and Diagnostic Research. 2015;9(3):ZC23. doi: https://doi.org/10.7860/JCDR/2015/11311.5652

4. Balaji TM, Varadarajan S, Jagannathan R, Mahendra J, Fageeh HI, Fageeh HN, et al. Melatonin as a Topical/Systemic Formulation for the Management of Periodontitis: A Systematic Review. Materials (Basel). 2021;14(9):2417. doi: https://doi.org/10.3390/ma14092417

5. Borysenko AV. Periodontal and Oral Mucosa Diseases. In 2 volumes. Kyiv: AUS Medicine Publishing; 2018. p. 224-253.

6. Cashman KD. Vitamin D Deficiency: Defining, Prevalence, Causes, and Strategies of Addressing. Calcif Tissue Int. 2020;106:14-2.
doi: https://doi.org/10.1007/s00223-019-00559-4

7. Ferlazzo N, Andolina G, Cannata A, Costanzo MG, Rizzo V, Currò M, et al. Is Melatonin the Cornucopia of the 21st Century? Antioxidants (Basel). 2020;9(11):1088.
doi: https://doi.org/10.3390/antiox9111088

8. Ghallab NA, Hamdy E, Shaker OG. Malondialdehyde, superoxide dismutase and melatonin levels in gingival crevicular fluid of aggressive and chronic periodontitis patients. Australian Dental Journal. 2016;61(1):53-61. doi: https://doi.org/10.1111/adj.12294

9. Hassan RS, Salman SA. Evaluation of salivary melatonin and periodontal parameters in type II diabetic patients with chronic periodontitis: A comparative study. Indian J of Public Health Research and Development. 2019;10(10):2740-5. doi: https://doi.org/10.5958/0976-5506.2019.03283.2

10. Konečná B, Chobodová P, Janko J, Baňasová L, Bábíčková J, Celec P, Tóthová Ľ. The Effect of Melatonin on Periodontitis. Int J Mol Sci. 2021;22(5):2390. doi: https://doi.org/10.3390/ijms22052390

11. Lodhi K, Saimbi CS, Khan MA, Nath C, Shukla R. Evaluation of melatonin levels in saliva in gingivitis and periodontitis cases: A pilot study. Contemp Clin Dent. 2016;7(4):519-23.
doi: https://doi.org/10.4103/0976-237X.194115

12. Permuy M, López-Peña M, González-Cantalapiedra A, Muñoz F. Melatonin: A Review of Its Potential Functions and Effects on Dental Diseases. Int J Mol Sci. 2017 Apr 19;18(4):865. PMID: 28422058;
PMCID: PMC5412446.
doi: https://doi.org/10.3390/ijms18040865

13. Ramesh A, Prakash A, Thomas B, Shetty M. Salivary melatonin and total antioxidant capacity in reproductive and postmenopausal women. Journal of the International Clinical Dental Research Organization. 2016;8(1):39. doi: https://doi.org/10.4103/2231-0754.176249

14. Sharan K, Lewis K, Furukawa T, Yadav VK. Regulation of bone mass through pineal-derived melatonin-MT2 receptor pathway. J. Pineal Res. 2017;4:63. doi: https://doi.org/10.1111/jpi.12423

15. Shariq N, Zohaib K, Sana Z, Muhammad S. Therapeutic potential of melatonin in oral medicine and periodontology. The Kaohsiung Journal of Medical Sciences. 2016;32(8):391-6.
doi: https://doi.org/10.1016/j.kjms.2016.06.005

16. Ternovoy NK, Drobotun OV, Kolotilov NN. Polymorbidity and heterogeneity of intact bone tissue in patients with malignant and metastatic bone tumors. Radiation Diagnostics, Radiation Therapy. 2019;3:25-29. doi: https://doi.org/10.37336/2707-0700-2019-3-3

Стаття надійшла до редакції
14.11.2021