Features of bone tissue metabolic processes in patients with generalized periodontitis in the period of disease exacerbation

I. P. Mazur
Institute of Stomatology at P. L. Shupik National Post-Graduate Medical Academy

Summary

Objective: Dystrophic and destructive processes in periodontal tissues as well as metabolic processes in bone tissue of the alveolar crest are closely related to the intensity of systemic metabolic processes and to the inner bone reorganization in the whole skeleton. Investigations revealed the influence of systemic factors (such as impaired homeostasis of main calcium-regulating hormones and disorders in bone tissue metabolism) on the activity of destructive and resorptive processes in the alveolar bone.

Materials and methods: 32 patients (18 women and 14 men) with generalized II–III° periodontitis in the period of disease exacerbation were examined clinically, roentgenologically and by laboratory testings. The control group included 13 patients in the initial grade of periodontitis or without clinical and roentgenological changes in periodontal tissues. Blood levels of the main calcium-regulating hormones such as parathyroid hormone and calcitonin as well as of the biochemical markers of bone remodeling processes (osteocalcin, bone-specific alkaline phosphatase, deoxypiridinolin and C-terminal telopeptide of type 1 collagen) were evaluated for every patient.

Results: A reliable increase in the serum levels of bone tissue resorption markers (deoxypiridinolin and C-terminal telopeptide of type 1 collagen) and a decrease of markers reflecting bone formation (osteocalcin, bone-specific alkaline phosphatase) was noted in patients with exacerbated generalized periodontitis as compared with the control group. A reliable increase in parathyroid hormone level and a tendency to an increase of the serum calcium level in the period of generalized periodontitis exacerbation was also determined.

Conclusion: Dissociation in the processes of bone tissue remodeling (i.e. prevalence of bone resorption and bone formation depression) was noted in patients with general periodontitis in the period of exacerbation. Destructive and resorptive processes in the alveolar bone during exacerbation periods of chronic generalized periodontitis were noticed to occur simultaneously with the periods of active bone tissue reorganization in the whole skeleton when bone resorption prevailed over osteogenesis.

Keywords: bone tissue, biochemical markers, periodontitis

Objective

Generalized periodontitis is a widespread health disorder characterized by gingival inflammation, formation of periodontal pockets and a progressing destruction of the
alveolar crest. Inflammatory and destructive processes in the periodontal tissue are caused both by local factors (such as microbial colonization, dental deposits) and by the general state of the organism, presence of systemic diseases. Analysis revealed a relationship between periodontal diseases and the structural and functional condition of the skeleton [3]. The processes taking place in the periodontal tissues and alveolar bone constantly interact with systemic processes in the whole organism, its organs and systems. As part of the skeletal system, the alveolar bone also reacts to eugenic and endogenic factors influencing the human organism. Metabolic processes in the alveolar bone are influenced by systemic hormones regulating calcium metabolism such as parathyroid hormone, calcitonin, calcitriol, estrogens, thyroxin and glucocorticoids. The condition of the skeletal bone tissue is determined by its mineral density and by activity of metabolic processes in the tissue. To evaluate the structural and functional state of bone tissue, diagnosing metabolic osteopathies and analyzing the effectiveness of osteotropic therapy, the method of ultrasound densitometry is used. Determination of bone tissue mineral density is the method of quantitative skeletal bone analysis enabling to evaluate the quantity of the minerals per volume unit. Using the methods of ultrasound osteodensitometry or uniphotone or biphotone absorbtivity, the state of the non-organic component of the bone (i.e. saturation of minerals and bone tissue density) is determined. Biochemical markers of bone remodeling processes are used to analyze changes in the organic bone matrix. The organic matrix consists of collagen (approximately 95%) and non-collagen proteins. Catabolic products of the organic bone components, enzymes of osteoblasts and osteoclasts, calcium and phosphate levels in biologic fluids are the markers of skeletal bone tissue remodeling [2]. Biochemical analyses enable determining the rates of bone tissue reorganization and the current activity of osteosynthesis and osteoresorption processes. Biochemical markers in combination with the measurement of bone mineral density are used to determine the intensity of metabolic processes and to control the effect of osteotropic therapy.

W. V. Gianobille [5] analyzed the biochemical markers of bone remodeling in the gingival fluid of experimental animals. Decreased levels of osteocalcin and C-terminal telopeptide of type 1 collagen as a marker of accelerated remodeling processes in the alveolar bone tissue was determined in dogs with experimentally induced periodontitis. In subsequent studies [6, 7] W. V. Gianobille revealed changes of these biochemical markers in patients with progressing periodontal diseases. Reliably increased levels of pyridinolin and C-terminal telopeptide of type 1 collagen in the gingival fluid were noted in the period of disease exacerbation with destruction of interdental septa.

This study aimed to estimate the activity of metabolic processes in bone tissue by evaluating the biochemical markers of bone remodeling in patients with generalized periodontitis in the period of exacerbation.

Materials and methods
32 patients (18 females and 14 males) with generalized II–III° periodontitis in the period of disease exacerbation were examined clinically, roentgenologically and using laboratory testings. The control group included 13 patients: 5 of them had no clinical and roentgenological changes in periodontal tissues and 8 patients had initial signs of the periodontal disease.

The clinical methods of examination included visual inspection of the oral cavity, estimation of the gingival bleeding, measurement of the periodontal pocket depth, evaluation of PMA index, Fiodorov–Volodkina oral hygiene index, Ramfierd’s index and the periodontal index. Roentgenological methods (such as orthopantomography, intraoral radiography and radiovisiography) were used for the examination of the alveolar process.

Laboratory investigation aimed to estimate the biochemical markers reflecting the condition of bone tissue metabolism and included evaluation of parathyroid hormone (in the morning), blood calcium, markers of bone tissue resorption (C-terminal telopeptide of type 1 collagen, deoxypyriddinolin with estimation of creatinine level in morning urine) and markers of bone tissue formation (bone-specific alkaline phosphatase, osteocalcin). Normal values for calcium level ranged from 2.15 to 2.55 mmol/l.

Serum parathyroid hormone level was determined by the immunological enzyme-intensified double-stage method using a DSL-10-80 ACTIVE I-PTH laboratory kit. The normal values of the parathyroid hormone level ranged from 16 to 62 pg/ml.

Evaluating the serum osteocalcin level, a double-centered enzyme-linked Osteometer BioTech A/S N-MID Osteocalcin One Step ELISA (Denmark) immunological test was used. The normal values for osteocalcin levels ranged from 5 to 55.8 ng/ml for men, from 4.9 to 30.5 ng/ml for pre-menopausal women and from 9.5 to 48.3 ng/ml for post-menopausal women.

Serum bone-specific alkaline phosphatase level was
Features of bone tissue metabolic processes in patients with generalized periodontitis in the period of disease exacerbation

determined by the enzyme-linked immunological method using a *Metra BAP ELA* kit (USA). The normal values for the level of this enzyme ranged from 15 to 41.3 U/ml for men, from 11.6 to 29.6 U/ml for pre-menopausal women and from 14.2 to 42.7 U/ml for post-menopausal women.

Evaluating serum C-terminal telopeptide of type I collagen level, the enzyme-linked *Serum CrossLaps ELISA* (Denmark) immunological test was used. Normal values for it ranged from 0.142 to 0.522 ng/ml for men, from 0.166 to 0.476 ng/ml for pre-menopausal women and from 0.251 to 0.761 ng/ml for post-menopausal women.

The deoxypyridinolin level was determined by the ratio to creatinine level in the urine using the enzyme-linked immunological method and a *Metra DPD ELA* kit (USA). The normal values for this ratio ranged from 3 to 7.4 nmolDpD/mmolCr for women (aged 25–44 years) and from 2.3 to 5.4 nmolDpD/mmolCr for men (aged of 25–55 years). Creatinine level was evaluated in the first portion of morning urine; normal values for the creatinine level ranged from 2.47 to 19.2 mmol/l for women and from 3.45 to 22.9 mmol/l for men.

The statistical analysis was performed using standard set of programs for the Microsoft Excel 2000 and Statistica-5 program.

**Results**

The present study, aimed to estimate the activity of metabolic processes in the bone tissue of the whole skeleton and locally in the alveolar bone in patients with generalized periodontitis in the period of its exacerbation revealed significant changes in the level of parathyroid hormone and biochemical bone remodelation markers. A reliable increase in serum parathyroid hormone level in patients with generalized periodontitis as compared with the control group was determined (Fig. 1). In patients with generalized periodontitis, the average parathyroid hormone level was 50.31 ± 3.56 pg/ml in women and 47.9 ± 4.32 pg/ml in men. In the control group average level of parathyroid hormone was 38.4 ± 5.64 pg/ml in women and 36.9 ± 3.46 pg/ml in men. 4 men in the analyzed group had parathyroid hormone levels exceeding upper border of the normal range (i.e. 62 pg/ml); the levels varied from 79.13 to 103.8 pg/ml. Parathyroid hormone stimulates bone tissue resorption by influencing the osteoclasts. An increased serum level of this hormone in patients with generalized periodontitis is an evidence of a systemic influence on the resorptive processes in bone tissue.

No reliable changes in serum calcium levels versus the normal range were revealed either in the test or the control group, either in men or in women. In generalized periodontitis patients, the average serum calcium level was 2.34 mmol/l in women and 2.35 mmol/l in men. In the control group, the average serum calcium level was 2.31 and 2.29 mmol/l respectively.

Evaluating the plasma concentration of biochemical bone remodelation markers, a reliable decrease of osteocalcin and bone-specific alkaline phosphatase levels related to the exacerbation of pathological process in periodontal tissues was revealed. Osteocalcin is a non-collagenic calcium-binding protein synthesized by osteoblasts and odontoblasts. By the results of multiple studies, the circulating osteocalcin level reflects bone formation rates. Evaluating serum osteocalcin level enables to diagnose metabolic osteopathies and to monitor activity of metabolic processes in bone tissue. In the period of generalized periodontitis exacerbation, a reliable decrease of osteocalcin levels in women of the test group was noted versus the control group women (average osteocalcin level was 22.65 ± 3.21 and 27.15 ± 4.18 ng/ml, respectively). A tendency to a decrease for the osteocalcin level was noted in men with generalized periodontitis as compared with the control group (average osteocalcin level in them was 28.1 ± 3.46 and 29.4 ± 4.32 ng/ml, respectively) (Fig.2).

Bone-specific alkaline phosphatase is produced by osteoblasts and contained in the bone tissue and in blood serum. Its blood level is determined by metabolic activity of the osteoblasts. Thus, blood concentration of this enzyme reflects the processes of bone formation and osteoid mineralization. This study, like studies performed by other authors, showed a reliable decrease of bone-specific alkaline phosphatase level both in men and women with generalized
periodontitis in the period of its exacerbation. In the test group, the average level of this enzyme was 21.36 ± 3.45 U/l in women and 17.71 ± 4.62 U/l in men. In the control group its average level was 30.4 ± 4.85 U/l in women and 34.7 ± 4.49 U/l in men (Fig. 3).

Decreased levels of the biochemical markers reflecting bone tissue formation (i.e. osteocalcine and bone-specific alkaline phosphatase) in patients with generalized periodontitis in the period of exacerbation is an evidence of decreased bone formation activity in the whole skeleton including the alveolar bone.

This study revealed reliably increased levels of the markers reflecting bone tissue resorption in patients with an aggravated course of generalized periodontitis (see Fig. 4 and 5). C-terminal telopeptide of type 1 collagen is a catabolic product of collagen, the main protein of the bone matrix. This marker correlates with the intensity of bone tissue resorption. A reliable increase of C-terminal telopeptide of type 1 collagen serum level was noted in the test group both in women (0.5439 ± 0.084 ng/ml) and in men (0.5525 ± 0.0967 ng/ml). In the control group, the average level of C-terminal telopeptide of type 1 collagen was 0.4135 ± 0.0783 ng/ml in women and 0.3321 ± 0.0862 ng/ml in men.

Deoxypiridinoline is mainly contained in bone tissue as part of bone collagen. It is released into the bloodstream due to bone resorption by the osteoclasts. Deoxypiridinoline is not metabolized in the liver, but is excreted in the urine. The most significant parameter for evaluating activity of the resorption processes in bone tissue is the ratio of deoxypiridinoline and creatinine concentrations in the urine. This study revealed a reliable increase of this ratio.
in patients with exacerbation of pathological processes in periodontal tissues. In the test group, the ratio of deoxypiridinoline and creatinine concentration in the urine was 11.451 ± 1.076 nmolDpD/mmolCr in women and 6.459 ± 1.23 nmolDpD/mmolCr in men. In the control group, this ratio was respectively 6.2 ± 0.978 and 3.89 ± 0.892 nmolDpD/mmolCr.

Increased levels of biochemical markers reflecting bone tissue resorption in patients with exacerbated generalized periodontitis, as compared with the control group, revealed a systemic amplification of destruction in the bone tissue of the whole skeleton. These changes are related to accelerated remodeling rates in the bone tissue (and also in the alveolar bone), depressed osteoblastic activity and intensified bone resorption. Clinical studies have revealed a close connection between the activity of pathologic processes in the periodontal tissues and metabolic processes in the skeletal system. Periods of generalized periodontitis exacerbation are related to a significant increase of parathyroid hormone level, intensive collagen desintergration and bone resorption processes and depression of new bone formation. Disbalance of bone tissue remodeling processes is general involves the whole skeleton and requires a systemic regulation of metabolic processes in bone tissue and administration of the osteotropic drugs as part of complex treatment in managing periodontal diseases.

Discussion

No common opinion was coined on the relationship between the general condition of skeletal bone tissue and the cause of periodontal diseases, because a close correlation between bone tissue mineral density and alveolar bone diminution rates was determined only in the postmenopausal women. The topicality of such studies is explained by the possibility to use osteotropic therapy in complex treatment of generalized periodontitis in case if this connection is confirmed. Our study revealed an impaired systemic metabolism of bone tissue in patients with generalized periodontitis in the period of its exacerbation. In this study, reliably increased serum levels of the markers reflecting bone tissue resorption (deoxypiridinolin and C-terminal telopeptide of type 1 collagen) and decreased levels of osteogenetic markers (osteocalcin, bone-specific alkaline phosphatase) were determined. A reliable increase of serum parathyroid hormone level and a tendency to an increased serum calcium level was also noted in the period of periodontal pathology exacerbation.

A 6-month pilot studies by Rocha (2001) revealed impaired metabolic processes in bone tissue and increased urine N-telopeptide level of type 1 collagen (it is another marker reflecting bone resorption) in patients with generalized periodontitis and type 2 diabetes mellitus. The use of alendronate in the complex treatment of these patients enabled to decrease N-telopeptide of type 1 collagen concentration. This fact, in authors’ opinion, is related to decelerated of bone tissue resorption.

Johnson (2002) analyzed the levels of estradiol and biochemical markers of bone tissue remodeling (osteocalcin and deoxypiridinoline) in sheep after ovarectomy. Increased osteocalcine levels and reliably increased deoxypiridinoline levels were noted. This fact, in authors’ opinion, is an evidence an accelerated rate of bone tissue remodeling. Changes of biochemical bone tissue remodeling markers and a decrease of mineral bone tissue density manifested earlier than a decrease of serum estradiol level in the experimental animals.

Another group of authors investigated the biochemical markers of bone remodeling locally in the site of the alveolar crest. Wilson (2003) offered a special method for taking alveolar bone and producing bone wash samples in which biochemical markers of bone remodeling (osteocalcin and N-telopeptide of type 1 collagen) were tested. The results of this study revealed a different activity of bone tissue remodeling in different sites of the alveolar bone. The levels of these markers evaluated in the alveolar bone samples significantly exceeded their blood concentration.

Thus, activity of metabolic (synthetic and destructive) processes in the bone tissue and the intensity of the inner bone reorganization are determined according to changes in the serum concentration of biochemical markers reflecting bone remodeling (formation and resorption). Dystrophic and destructive processes in periodontal tissues as well as metabolic processes in bone tissue of the alveolar crest are closely related to the intensity of systemic metabolic processes and inner bone reorganization in the whole skeleton. Exacerbation of generalized periodontitis and aggravation of destructive and resorptive processes in the alveolar bone are combined with the depression of new bone formation and intensified bone tissue destruction in all parts of the skeleton. Destructive and resorptive processes in the alveolar bone during exacerbation periods of chronic generalized periodontitis were noticed to occur simultaneously with the periods of active bone tissue reorganization in the whole skeleton when bone resorption prevails over osteogenesis. Destructive and
resorptive processes in the alveolar bone are caused not only by the local factors (such as microbial colonization and inflammatory processes of the oral cavity), but also by the systemic influence of some hormones and metabolic processes in the skeletal system. Systemic methods of treatment, influencing the metabolic processes in bone tissue (such as osteotropic drugs) are necessary to use in generalized periodontitis patients in order to correct the pathologic processes in the alveolar bone. Evaluation of biochemical bone remodelation markers is also necessary for a more precise administration of osteotropic drugs and monitoring their effectiveness.

Conclusion
A complex (clinical, roentgenological and laboratory) investigation of 32 patients with generalized periodontitis and 13 patients without clinical and roentgenological signs of periodontitis or with initial symptoms of this disease revealed an impaired systemic metabolism of the bone tissue and an increased secretion of parathyroid hormone in patients with general periodontitis in the period of its exacerbation. A disbalance of bone tissue remodeling processes was determined: a reliable increase of biochemical markers reflecting bone tissue resorption (deoxypiridolin and C-terminal telopeptide of type 1 collagen (ICTP)) as markers of rapid bone turnover in periodontitis. A pilot study in beagle dogs. J Clin Periodontol. 1995; 22(12): 903–10.

References
3. Поворознюк ВВ, Мазур ИП. Костная система и заболевания пародонта. К: 2003: 446.

Received 12 September, 2006
Accepted 27 November, 2006
Features of bone tissue metabolic processes in patients with generalized periodontitis in the period of disease exacerbation

Kontrolinę grupę sudarė 13 ligonių, sergančių pradinės stadijos periodontitu, arba ligoniai, kurių periodonto audiniai kliniškai bei rentgenologiskai nepakito. Kiekvienam ligoniui buvo įvertinta svarbiausių kalcio lygį reguliuojančių hormonų priešskydinės liaukos hormono bei kalcitonino ir biocheminių kaulo remodeliavimo procesų žymeklių (osteokalcino, kaulo specifinės šarminės fosfatazės, deoksipiridolino ir C-terminalinio 1-ojo tipo kolageno telopeptido) kraujo koncentracija.

Rezultatai: Ligonių, sergančių paūmėjusiu periodontitu, lyginant su kontroline grupe, kaulo formavimą atspindinčių rodiklių (osteokalcino, kaulo specifinės šarminės fosfatazės) koncentracija buvo mažesnė. Taip pat pastebėta patikimai didesnė priešskydinės liaukos hormono koncentracija ir plazmos kalcio koncentracijos didėjimo tendencija.

Išvados. Ligoniams, sergantiems paūmėjusių bendrojo periodontitu, aptikta kaulo audinio remodeliavimo procesų disociacija, t.y. kaulo rezorbcija vyravo, lyginant su kaulo formavimu. Destrukciniai ir rezorbciniai procesai vyko kartu su aktyvia viso skeleto kaulų audinio reorganizacija.

Raktažodžiai: kaulinis audinys, biocheminiai žymenys, periodontitas