Case report

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Weekly alterations in bone mineral density in the Gruen zones after total hip arthroplasty (clinical case and brief literature review)

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Introduction Dual-energy X-ray absorptiometry (DEXA) provides a quantitative estimation of the projectional bone mineral density (PBMD) with minor radiation exposure and in a cost-effective way. It is one of the ways for a dynamic control of stem integration into the host bone after total hip arthroplasty (THA). Osteocytes are considered to play the key role in the regulation of implant integration process. Hence, DEXA could be used for estimation of functional activity and directions for regulation of osteocytes activities in the periprosthetic area. **Purpose** Current study presents the results of chronologic and biological PBMD in the periprosthetic zone after THA in two patients with a perspective for a future use of such an approach to reveal a local response of tissue to the implant. **Material and methods** PBMD was studied daily for 10 days with PRODIGY densitometer after THA in a 54-year old patient with posttraumatic right hip osteoarthrosis and a 59-year old patient with right femoral neck fracture nonunion. Cementless ZIMMER implants were used. **Results** In the first patient, oscillatory BMD alterations in the Gruen zones ranged from 2.4 to 11.6 % with an average wavelength of 4.6 days. In the second patient, the alterations were within the range of 2.3–8.7 % with an average wavelength of 4.5 days. PBMD changes in the adjacent Gruen zones occurred asymmetrically with some oscillational phase lagging relative to each other. After approximation of the results by linear trend, PBMD increased by 1.7 % on average in all Gruen zones in the first patient, except zones 2 and 3, and its mean growth was 1.7 %. On the contrary, PBMD decreased in all the zones in the second patient, except zones 4 and 7. Mean decrease was 1.7 %. **Conclusion** Chronobiological approach opens up possibilities for evaluation of structural and functional skeleton reorganization in the periprosthetic zone after THA. Further research is needed for a deeper insight into this complex issue.

Keywords: bone tissue, mineral density, hip joint, arthroplasty, biorhythms of a mineral exchange, Gruen zones

INTRODUCTION

Studies on the molecular biology and osteocyte function that were conducted in the last decades show that these amazing cells are not "passive bone fillers". They have numerous functions, including initiation of osteoclast-osteoblastic remodeling, control of the activity of osteoclasts and osteoblasts, endocrine function and synthesize the growth factor of fibroblasts 23. In addition, osteocytes directly participate in the metabolism of bone tissue, remodeling their perilacunar matrix (**Fig. 1** and **2**) [1, 2, 3]. The lifespan of these cells is 10-20 years [4]. The functional capacity of the osteocyte pool decreases as the organism ages. The proportion of dead cells increases, the lacunae of which become filled with mineralized tissue (micropetrosis) [5][1].

The ability of osteocytes to remodel the surrounding matrix was shown in studies of various vertebrate species, including bats, hamsters, squirrels, rats, rabbits, snakes, eels, salmon, carp, and reptiles. In addition, it was established that remodeling of the matrix that surrounds osteocytes was activated under the the mobilization of minerals from the skeleton, for example, during lactation, hibernation, and physiological conditions that require an increase in pregnancy [6].

[1] More detailed achievements in the field of molecular biology and the function of osteocytes in recent decades were presented in a special issue # 54 of Bone (2013) titled “Osteocyte”

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Osteocytes contain receptors of the hormones of the parathyroid gland, ovaries, adrenals, etc. [7, 8, 9], being a target cell for these systemic regulators. Moreover, osteocytes ensure the flow of calcium from the bone matrix into the bloodstream [10], that is, their functions represent the nodal element of the system for maintaining the parameters of the body's mineral homeostasis [11, 12, 13, 14]. The latter is due to the fact that osteocytes exist within the lacunar-canal system which has a huge surface for ions exchange. The cytoplasmic processes of the cells are connected to each other, as well as to the cells covering the surface of the bone, and with the osteoblasts form a network of syncytium throughout the skeleton which allows transport of substances from anywhere in the skeleton [15, 16, 17]. The density of osteocytes varies between 10,000–20,000 in 1 mm^3 [4, 18, 19, 20].

The foregoing shows that there is an urgent need to develop a non-invasive method for assessing the functional state of osteocytes. Experimental studies of mineral metabolism of bone structures using various methods, including microdensitometry of radiographs, biochemical determination of the level of mineral phosphates and determination of ^{32}P with the radionuclide technology that were previously conducted showed that the concentration of the mineral component of bone tissue fluctuates with circaseptan periodicity (weekly) [21, 22, 23].

Taking into account the results of the studies, as well as the data of other authors [8, 24, 25, 26, 27, 28, 29], a hypothesis has been advanced, according to which, these short-term (circaseptan) fluctuations in mineral density are associated with osteocytic bone tissue remodeling [23] what is ***a morphologically confirmed permanently functioning phase physiological process that provides deposition and resorption of the pereosteocytic bone matrix*** [30].

Second, a noninvasive control of the activity of osteocytic remodeling can be carried out by the method of dual-energy X-ray absorptiometry (DEXA). The choice of this method is associated with insignificant radiation exposure [31, 32], a relatively short study time, sufficient sensitivity to detect such fluctuations [31, 33], and low financial burden. Previous studies made it possible to optimize the algorithm for estimating the projected bone mineral density (PBMD) and to limit the reproducibility error (precision) to clinically permissible boundaries < 1 % [34, 35, 36].

To confirm the possibility of using DEXA for the purpose of dynamic PBMD control, a study of volunteers was conducted in which the PBMD was estimated daily for 30 days (**Fig. 3**) [33, 37, 38, 39]. The obtained data indirectly confirmed that DEXA is able to quantify short-term fluctuations in PBMD. Thus, according to the hypothesis, the functional state of osteocytes can be monitored. In favor of the latter, the fact that the whole cycle of replacement of bone areas by osteoclastic-osteoblastic remodeling is 130 days or more while the phase of resorption with the participation of osteoclasts continues 27 or more days [40]. Thus, it is doubtful that osteoclastic-osteoblastic remodeling can make a significant contribution to the occurrence of weekly PBMD fluctuations.

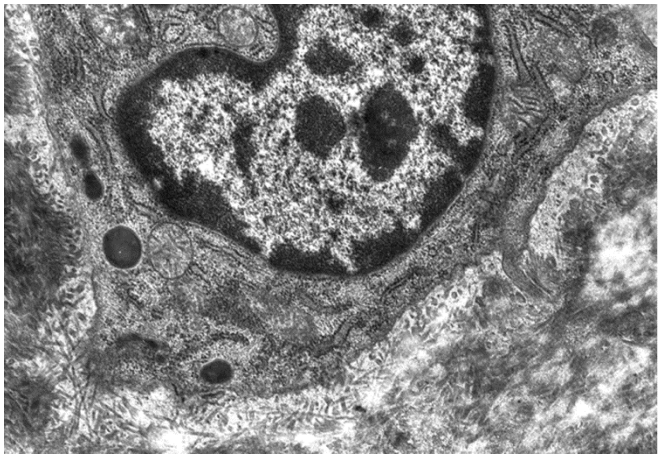

Fig. 1 Fragment of an osteocyte with a developed protein-synthesizing apparatus. There are numerous collagen fibrils in the peri-cellular space. The osmiophilic line is absent. TEM; magnification × 11000

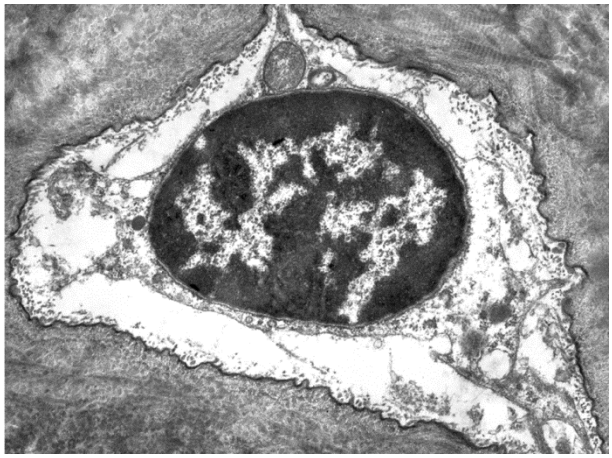

Fig. 2 Osteocyte with an enlarged pericellular space in the bone lacuna with uneven edges. The osmophilic line is not distinctly expressed everywhere. TEM; magnification × 11000

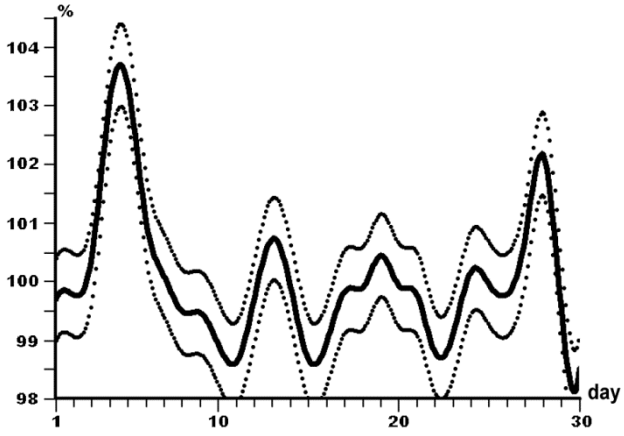

Fig. 3 Mathematical statistical modeling of dynamic changes in the PBMD of the left forearm (total area) according to the results of the study of volunteers with the DEXA method [37]. Vertical axis are values of PBMD in %; horizontal axis are study periods in days. ***Notes*** ——— – oscillatory curve with parameters of model P = 0.9; ····· – half-width of the confidence strip (1.96 × σσ)

Such monitoring is necessary from the clinical point of view in contemporary orthopedics. The example is a non-invasive evaluation of the integration processes that occurs during the interaction of the "bone-implant" system after hip joint replacement surgery. This operation is a widely used and effective method of surgical recovery of the locomotor functions in the lower limbs.

Considering the above discussed, the Russian R.R. Vreden NIITO conducted the study on the PBMD dynamics in the periprosthetic zone after hip arthroplasty with the use of chronobiological methodology. In this paper, we present two clinical observations illustrating the short-term changes in PMBD in the Gruen zones which are related, in our opinion, to the integration process of the implant stem with bone structures.

MATERIAL AND METHODS

Patient 1, 54 years old, was admitted to the Vreden NIITO in a planned manner with a diagnosis: posttraumatic right side coxarthrosis in stage 3. After a comprehensive examination, total right hip arthroplasty with the ZIMMER implant and cementless fixation of both components was performed (**Fig. 4A**). The duration of the intervention was 1 hour 45 minutes. Spinal anesthesia was used. The stitches were removed on the 12th day and the patient was trained to walk with crutches. The patient was discharged 18 days after the operation for an outpatient treatment in a satisfactory condition.

Patient 2, 59 years old, was admitted to the Vreden NIITO in a planned manner with a diagnosis: nonunion of the right femoral neck with the presence of metal structures. After a comprehensive examination, total hip arthroplasty with the ZIMMER implant and cementless fixation of both components was performed (**Fig. 4B).** The duration of the intervention was 1 hour 45 minutes. Spinal anesthesia was used. The postoperative period was uneventful. The patient was trained to walk with crutches. Sutures were removed on the 15th day. The patient was discharged in a satisfactory condition 14 days after the operation for an outpatient treatment.

PMBD estimation in the periprosthetic zone The study was performed using the PRODIGY digital densitometer (GE Medical Systems LUNAR) daily from 9 a.m. to 10 a.m. for 10 days. Daily densitometric scanning of the periprosthetic zone was repeated five times with an interval of 2-4 minutes. To prevent significant deviations of PMBD, patient's positioning was strictly controlled by the radiologist.

Voluntary informed consent of patients We conducted a previous study of the radiation exposure [32], according to which the dose of external exposure to humans during the densitometry procedure on a digital densitometer PRODIGY (GE Medical Systems LUNAR) was proved to be relatively small and corresponds to the average level of the natural exposure of a person per one day [31, 32]. These data were presented at the meeting of the Committee on Ethical Examination of Clinical and Experimental Research on the base of the FGBU R.R. Vreden NIITO Clinic. Permission was obtained to conduct densitometric studies on patients. The patients gave a written consent to participate in this study after having been completely informed on the procedure.

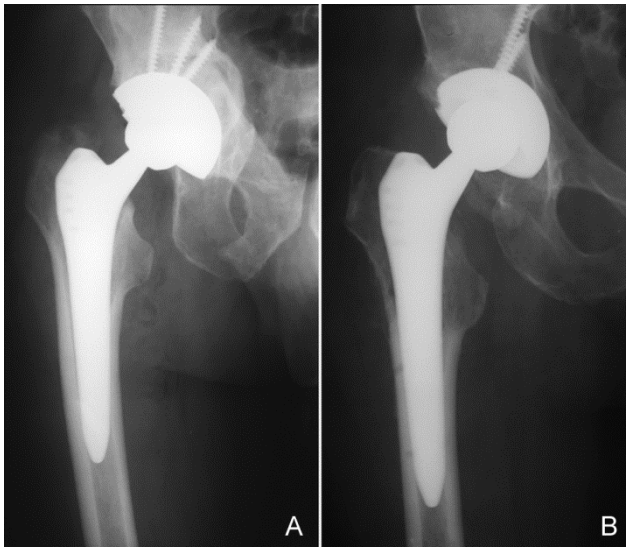

Fig. 4 Radiographs of the right hip joint after THA with the ZIMMER implant and cementless fixation of both components. X-rays: **A** – patient 1; **B** –patient 2

Statistical data processing Based on the results of the study, the mean values of PMBD in each Gruen zone were calculated, and then the data of each examination were recalculated as a percentage of this value. The Wilcoxon-Mann-Whitney U-test was used to test the hypothesis of two samples homogeneity (differences in the mean trends for independent samples).

Statistical mathematical modeling Based on the results obtained in the study for each Gruen zone, dynamic rows were formed that were approximated by a fourth-order polynomial spline and statistical mathematical models of the curve with approximation parameters $p = 0.97$ (significance level $P < 0.05$) were constructed. In addition, to determine the general orientation of changes in bone architecture in each Gruen zone, the dynamic rows of data were approximated by a rectilinear trend.

RESULTS AND DISCUSSION

Patient 1 The maximum range of PBMD deviations in the Gruen zones varies and ranges from 2.4 to 11.6 % (average, 5.3 %). Within these limits, the changes in this index occurred in the oscillatory mode (**Fig. 5**). The average wavelength was 4.6 days, or it corresponds to the length of circaseptan fluctuations (7 ± 3 days). The oscillation parameters are shown in the table. The nature of these oscillations differs between the zones. It is noteworthy that in the neighboring zones the oscillations are in anti-phase. So, if the process of reorganization begins with the growth of PBMD in zone 1, then in zone 2 it starts with a fall. Similar differences are observed between zones 6 and 7. These data indicate a certain asymmetry in the processes of reorganization of bone structures between neighboring Gruen zones. This is also evidenced by the fact that the extremes of the waves were evenly distributed throughout the time interval of the study.

Patient 2 The maximum range of PBMD deviations in the Gruen zones varied and was within the limits of 2.3 to 8.7 % (average, 5.5 %). Within these limits, the changes in the index occurred in the oscillatory regime (**Fig. 6**). The average wavelength was 4.5 days. It corresponds to the length of circaseptan oscillations (7 ± 3 days). The oscillation parameters are shown in the table. The nature of these oscillations differs between zones. It is noteworthy that, as in Patient 1, fluctuations of PBMD in the neighboring zones, are in anti-phase. So, if the process of reorganization begins with the growth of PBMD in zone 2, then in zone 4 it starts with the fall. Similar differences are observed between zones 7 and 4. These data indicate a certain asymmetry in the processes of reorganization of bone structures between neighboring Gruen zones. This is also evidenced by the fact that the extremes of the waves are distributed over the entire time interval of the study.

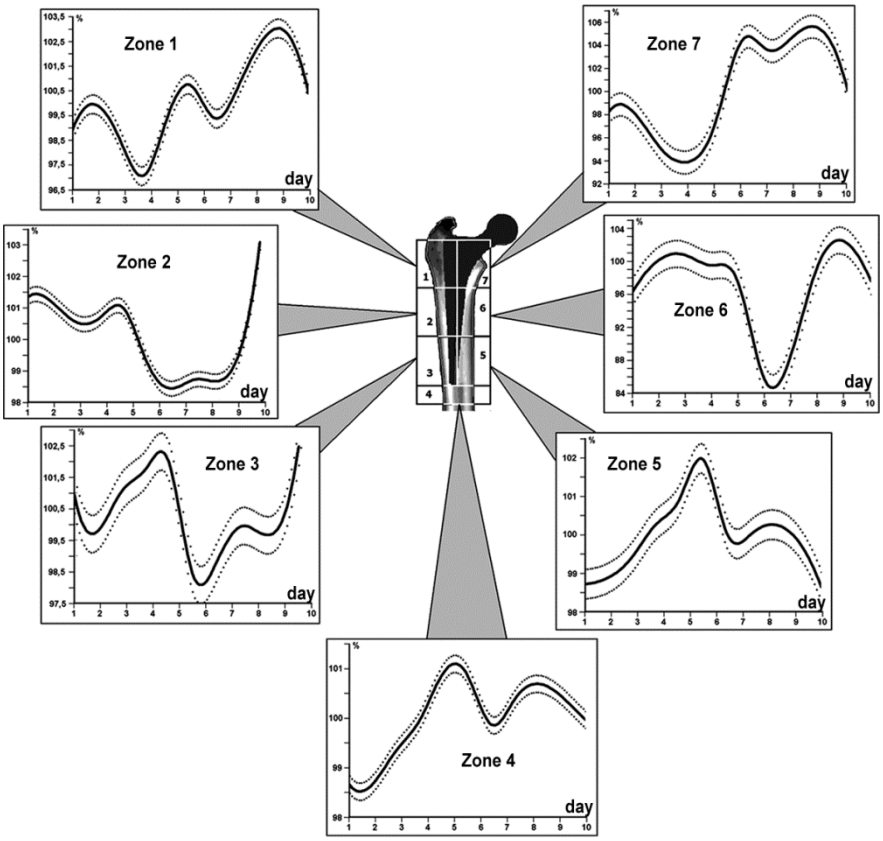

Fig. 5 Results of statistical mathematical modeling of PBMD dynamics in the bone structures in patient's 1 Gruen zones. Designations: on the horizontal axis – the time elapsed since the operation; on the vertical axis – PBMD in %; ——— – approximation of the results of the smoothing spline immediately after the operation (model parameters p = 0.97, significance level $P < 0.05$); ····· – half-width of the confidence strip ($1.96 \times \sigma$)

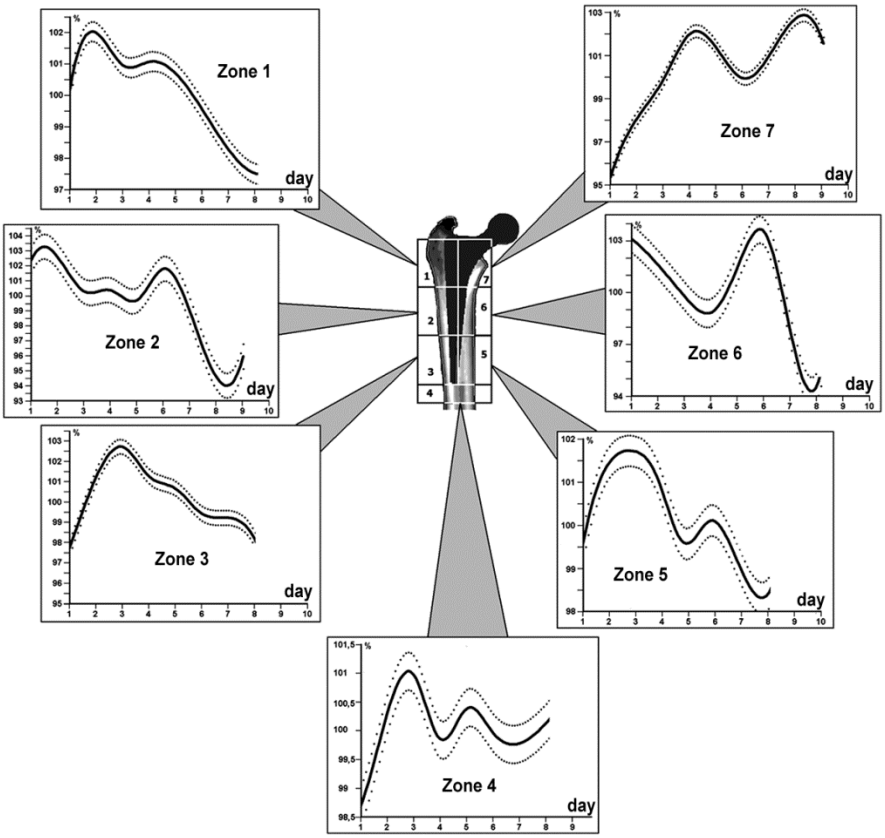

Fig. 6 Results of statistical mathematical modeling of PBMD dynamics of bone structures in the Gruen zones in patient 2

In our opinion, the asymmetry effect of the change in PBMD results from the alternate predominance of anabolic and catabolic processes (resorption and formation of bone tissue) in the neighboring Gruen zones, according to the law of intermittent activity of the functioning structures.

This law was formulated by G.N. Kryzhanovsky [41, 42]. He noted that when physiological functions are performed, the working structures constantly switch on and off. This is carried out by the mechanisms of autoregulation after reaching some critical level of the work performed. The law is essential for maintaining the normal state and maintaining the dynamic homeostasis of cells and the working organ as a whole. It acquires a particular importance in the conditions of increased functional load. If the structures did not function in accordance with this law, they could not restore their plastic and energy potential under prolonged intensive workload, which would lead to depletion of reserve capacities, energy and plastic deficiency in cell structures and, ultimately, to dystrophy and progressing decrease in the level of functional activity of some tissue, organ, etc.

Wavy PBMD changes in the periprosthetic zone, in fact, reflect a gradual reorganization of the skeleton architecture by alternating the predominance of bone structures formation and resorption. This reorganization is a local response of the body to the changes of the mechanical environment in the periprosthetic zone resulting from joint arthroplasty. To determine the general orientation of this process, the results of the study were approximated by a rectilinear trend, and then a quantitative assessment of trend changes was made by calculating the difference between the trend values at the beginning and at the end of the study. As can be seen from the graph (**Fig. 7**), in patient 1, the trend increase in PBMD occurs after the operation in Gruen zones 1, 4, 5, 6 and 7 while in 2 and 3 there is a decrease. On average, the trend increase in PBMD was 1.7 % in the periprosthetic zone. In patient 2, on the contrary, a decrease is observed in zones 1, 2, 3, 5, 6 while in zones 4 and 7 there is an increase. Thus, it can be said that the fluctuation changes in PBMD in the periprosthetic region in the majority of Gruen zones in patient 1 lead to an increase in mineral density, and in patient 2 to a decrease.

In addition to osteocytic remodeling, short-term PBMD fluctuations in the periprosthetic zone can also be caused by the nanoscale mechanism that has been recently discovered and that causes a low-energy shift of the unfilled valence states of Ca^{2+}, PO^{3-} and OH^{-}- ions in the bone tissue compared to their energy in the hydroxyapatite mineral [43, 44]. The nature of this shift is due to the fact that the nanocrystallites of hydroxyapatite in the mineral matrix form orderly co-planar conglomerates. The appearance of this over-ordering in comparison with the mineral is the source of the low-energy conglomerate-crystal shift.

Spectral roengenological studies of bone tissue performed using monochromatic synchrotron radiation in the MAX IV laboratory of Lund University (Sweden) and at Helmholtz Center in Berlin (Germany) using the equipment of the UE56/2 and RGBL channels of the BESSY II synchrotron, confirmed the appearance of this conglomerate-crystal shift [44]. This shift is proportional to the ratio of the width of the hydrate layer in the co-planar conglomerate of nanocrystallites to their characteristic size [43, 44]. A possible result of these local changes is an increase in the diffusion of calcium ions from nanocrystallites into the extra-crystalline space (lacunar-canal system) and, further, under the influence of the osteocyte pump, into the bloodstream. This mechanism can, on the one hand, cause changes in PBMD, and on the other hand, participate in maintaining a balance of relations between the mineral matrix of bone tissue and extracellular fluids.

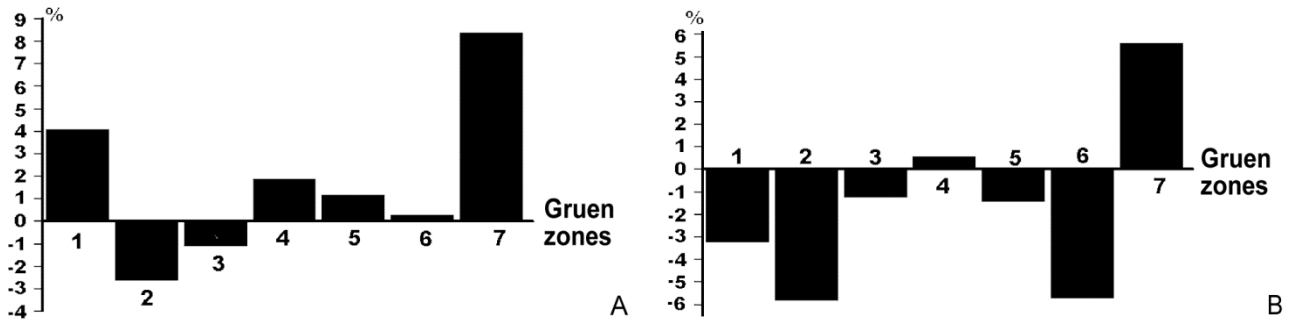

Fig. 7 Nature of the trends in the PBMD changes in the Gruen zones. Vertical axis: difference in mineral density between the beginning and the end of trend changes; horizontal axis: the zones of Gruen. Graph **A** – patient 1, graph **B** – patient 2

CONCLUSION

The results of the first study of the PBMD dynamics in the Gruen areas after hip arthroplasty using chronobiological methodology, illustrated by two clinical observations, show that the integration of the implant stem with bone structures proceeds in an oscillatory mode with a wavelength of about a week. Thereby, the processes of mineralization and demineralization in the neighboring areas proceed asymmetrically, i.e., if there is an increase in mineral density in one of the zones, then in the neighboring zone there happens the fall and vice versa. This indicates that the integration of the implant into bone structures proceeds step by step; and newly formed bone structures undergo further destruction, and the new ones are constructed in their place that from a mechanical point of view function more optimally. Such a process is similar to reparative osteogenesis in the fracture zone, where a gradual adjustment of the architecture of bone structures to a changing mechanical environment occurs until they reach functional maturity.

The presented data confirm the possibility of using the chronobiological methodology by densitometric control of mineral density for a non-invasive assessment of the "bone-implant" integration in clinical conditions and in the short-term time interval. In our opinion, this direction is promising, but requires further research and details of the methodological approach under consideration. Then, it will become possible to use the DEXA method to test the functional state of bone cells in clinical practice.

Table

Chronobiological features of PBMD changes in Gruen zones

Gruen zone	Number of waves	Wavelength* (days)	Maximum and minimum (days)	Absolute range of PBMD deviations (%) in the study period
Patient 1				
1	2	First wave – 3 Second wave – 4	1 5	6.2
2	2	First wave – 4 Second wave – 6	3 6	2.9
3	2	First wave – 4 Second wave – 4	1 6	4.2
4	2	First wave – 5 Second wave – 3	1 7	2.4
5	1	First wave – 7	5	3.6
6	1	First wave – 6	2	6.4
7	2	First wave – 6 Second wave – 3	3 7	11.6
Mean		Mean = 4.6 MSE = 1.4	–	Mean = 5.3 MSE = 3.2
Patient 2				
1	1	First wave – 3	2	4.4
2	1	First wave – 4	1	8.0
3	1	First wave – 6	2	5.0
4	2	First wave – 4 Second wave – 3	2 5	2.3
5	1	First wave – 5	2	2.9
6	1	First wave – 5	3	8.7
7	1	First wave – 6	4	7.4
Mean		Mean = 4.5 MSE = 1.2	–	Mean = 5.5 MSE = 2.5

Note: The last wave of change in PMTCT in each Gruen zone was not taken into account as it did not end during the study period

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