Assessment of Parathyroid Hormone Serum Level as a Predictor for Bone Condition Around Dental Implants

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Purpose: *The aim of this prospective study was to evaluate parathyroid hormone serum level as a potential single factor of bone metabolism around dental implants.* ***Materials and Methods:*** *Parathyroid hormone levels were measured before implantation. Intraoral digital radiographs were taken in standardized conditions in all cases: immediately after implantation, immediately after functional loading, and 3, 6, 9, 12, 18, and 24 months after functional loading. The next phase was to align all radiographs geometrically. Two regions of interest were marked in the bone image: one in the implant neck region and another in the periapical region. Next, the entropy of the microarchitecture of the bone image was calculated, and an analysis of simple regression was performed.* ***Results:*** *The prospective study included 107 patients of both sexes in the age range of 17 to 67 years (mean ± SD: 45.53 ± 12.1 years). A significant relationship was observed between higher levels of parathyroid hormone (but still in the normal range) and the decrease of textural entropy in the alveolar ridge bone at 3, 6, 12, and 18 months after functional loading. However, in the periods immediately after implantation, immediately after functional loading, and 9 and 24 months after functional loading, the relationship was not statistically significant.* ***Conclusion:*** *Assessment of the parathyroid hormone serum level can be considered a useful method to predict bone condition around a dental implant, but not as a single factor.* Int J Oral Maxillofac Implants 2017;32:e207–e212. doi: 10.11607/jomi.5686

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In this era of rapidly developing implantology, scientists are still searching for better ways to assess factors that could predict the long-term success of dental implant therapy. Disorders in metabolic bone turnover parameters are common in humans and are often asymptomatic. In those cases, only specific laboratory tests can detect certain pathologies or anomalies, and thus, reduce the risk of failure in dental implant therapy.

The parathyroid hormone is secreted by the chief cells of the parathyroid glands. Parathyroid hormone is a polypeptide composed of 84 amino acids. The biologic activity of the parathyroid hormone is related to the structure and sequence of the first 34 amino acids of the N-terminal fragment.[1] Parathyroid hormone plays an important role in bone metabolism and remodeling. Normal serum parathyroid hormone levels range from 10 to 60 pg/mL. The concentration of ionized calcium in blood serum is a primary regulator of parathyroid hormone secretion; ie, hypercalcemia decreases and hypocalcemia increases parathyroid hormone synthesis. Parathyroid hormone influences bone tissue, kidneys, and intestines by causing increases of ionized calcium and decreases of inorganic phosphate serum concentration. In kidneys, parathyroid hormone decreases excretion of ionized calcium and increases excretion of inorganic phosphates with urine. Parathyroid hormone enhances the release of calcium from the bone reservoir and increases the activity of alkaline phosphatase in blood. Moreover, parathyroid hormone indirectly enhances the absorption of calcium in the intestines, leading to the stimulation of calcitriol formation. Parathyroid hormone also inhibits reflexive resorption of inorganic phosphates in proximal kidney tubules (increase of inorganic phosphate

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excretion) and increases inorganic calcium resorption primarily in distal kidney tubules (decrease of inorganic calcium excretion).

One of the most common assessment methods of dental implantation complications is radiologic examination.[2] The same technique is used for monitoring guided bone regeneration.[3] Finding the relationship between the parathyroid hormone serum concentration and the textural entropy of marginal crestal bone could be helpful in reducing dental implant failure. The utility of this type of analysis was confirmed in a recent study.[4]

The aim of this prospective study was to evaluate parathyroid hormone serum level as a potential single factor of bone metabolism around dental implants. Additionally, the potential relationship between the textural entropy of marginal crestal bone and the parathyroid hormone serum concentration was examined.

MATERIALS AND METHODS

Ethical board permission was received (no. RNN/27/12/KE). The inclusion criteria were: no metabolic diseases, no autoimmune diseases, and visualization of the implant in full length on a radiograph. The exclusion criteria were: no response in follow-up examination, diagnosed metabolic or bone disease before the investigation, and drug affecting bone metabolism. All patients signed a written consent after receiving information about the content of the study. Parathyroid hormone levels were measured before implantation (blood samples from the ulnar vein were collected on an empty stomach at approximately 8 a.m. for a radioimmunoassay test). Intraoral digital radiographs were taken in standardized conditions in all cases: immediately after implantation, immediately after functional loading, and 3, 6, 9, 12, 18, and 24 months after functional loading. Prosthetic restorations were cemented to abutments. Radiographs were taken during typical clinical follow-ups. The straight-angle technique for radiographs was used. Scans were made by the Focus X-ray device (Instrumentarium Imaging). The Digora system for sensor plates was used (Soredex, Orion Corporation), and an analog system of image editing was excluded. The active part of recording plates was the selenium layer. The size of the radiograph point (pixel) was 70 $\times$ 70 µm.[5] Images were completed by a standardized technique.[6] The exposure time was 0.1 seconds with an intensity of 7 mA and a constant voltage of 70 kV.[5] After the exposition sensor plates were scanned, the images were provided to the database archive of Digora for Windows 1.51.[7] A silicone putty mass was used repeatedly to set the sensor. The film-fixing bracket was set up by mass and, when the mass became hard, radiographs were taken. Next, the mass was removed from the holder and stowed. A note about the patient data was kept in the archive until the next appointment. Through the use of this method, images showed minor inaccuracies.

In the next step, images were normalized electronically. The first phase of research before dental image analysis was a geometrical normalization of radiographs. Even slight distortions were eliminated. Every picture for the same patient was aligned to its direct postimplantation radiograph. In digital geometric standardization, pairs of topographic pointers were placed. Landmarks were used in the same anatomical positions around dental implants (10 points) on the twin pictures of the same person. ToothVis 1.6 software (Department of Information Technologies, University of Maria Curie-Sklodowska) was used to eliminate the deformations.[8,9] The process and quality of normalization was verified by Dental Studio (Flipper and Subtraction functions). The Flipper function caused alternate bounded manifestation control and aligned the images. When points were moving (due to movement of the implant image), the alignment had to be revised and corrected by the Geometric Alignment function, and afterward confirmed by subtraction.[10] If the dental images were correctly matched, the area of the implant disappeared, and only the prosthetic device was visible in the subtraction image. When the radiograph of the same patient included several implants, it was not possible to standardize them altogether. Each implant was corrected separately, which significantly increased the precision of the normalization. By compensating the deformation markers around implants on the radiographs of the same patient in a follow-up visit, the results were demonstrated to be the same. Two regions of interest, one in the implant neck region and the other in the periapical region, were marked in the bone picture (Fig 1). Anatomical structures such as the mental foramen, the incisive foramen, the alveolar ridge of the maxillary sinus, and the roots and crowns of the teeth were not marked to avoid overlap with a region of interest. For this objective, MaZda 4.5 software (Institute of Electronics, Technical University of Lodz, Poland) was used. To diminish initial noise, 8-bit radiographs were converted to 7-bit images. The pictures had previously standardized region of interest analogs for following radiographs of the same patient and monitoring the region of interest marked digitally; these pictures were compared and analyzed. The textural entropy parameter was analyzed as a feature that responds to the formation of mature trabecular bone (Fig 2).[9,11] Next, the relation between parathyroid hormone serum concentration and entropy of the microarchitecture of the bone image was analyzed. Analysis of regression was performed using

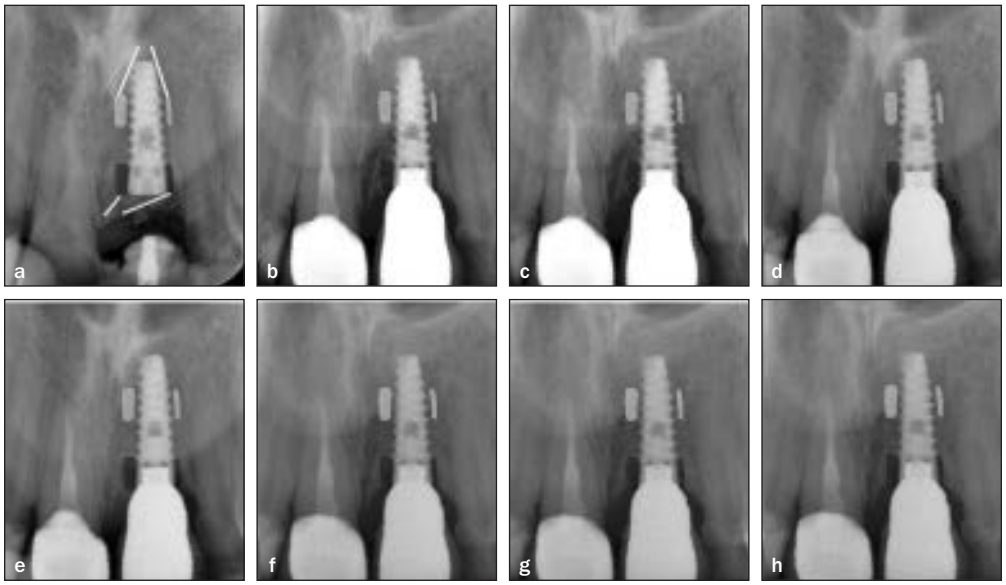

Fig 1 Series of analyzed radiographs with the implant neck region and the periapical region marked: *(a)* implantation; *(b)* immediately after functional loading; *(c)* 3 months after functional loading; *(d)* 6 months after functional loading; *(e)* 9 months after functional loading; *(f)* 12 months after functional loading; *(g)* 18 months after functional loading; *(h)* 24 months after functional loading.

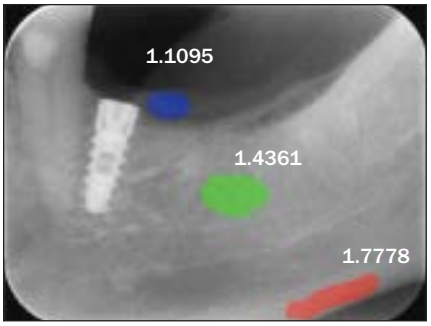

Fig 2 Values of entropy of soft tissues, trabecular bone, and cortical bone.

StatgraphicsCenturion XIV software (StatPoint Technologies). The level of significance was $P < .05$.

RESULTS

One hundred seven patients of both sexes in the age range of 17 to 67 years (mean ± SD: 45.53 ± 12.1) were included in the study. In total, 249 dental implants of different types were placed. Six different types of implants were used. The most used was MIS (Seven, Biocom; n = 157), followed by Alpha-Bio (SPI, SFB, ATI, DFI; n = 45), AB (i5; n = 24), Wolf (ForMe; n = 8), OSSTEM (GS3; n = 8), and lastly, Dentsply (Ankylos C/X; n = 7). Twenty-five patients with 50 dental implants placed showed raised parathyroid hormone serum concentration (but still in normal range). One patient with five dental implants had a decreased parathyroid hormone serum level. Parathyroid hormone serum levels ranged between 3 and 97.9 pg/mL. Higher levels of parathyroid hormone serum concentration (high normal) were related to a decrease in the textural entropy of marginal crestal bone 3, 6, 12, and 18 months after functional loading (Fig 3).

The relation between parathyroid hormone serum level and textural entropy of marginal crestal bone was not statistically significant in the following periods: directly postimplantation, directly after functional loading, and 9 and 24 months after functional loading (Tables 1 and 2).

DISCUSSION

To the authors' knowledge, so far this is the largest group of subjects with dental implants and intraoral radiographs combined with parathyroid hormone serum tests in the Polish population. To date, there have been no clinical reports with evaluation of parathyroid hormone serum concentration before dental implantation. Moreover, existing articles address recombinant parathyroid hormone. The results of the present study suggest that, the higher the parathyroid hormone serum concentration level, the lower the level of textural entropy. In such a state, diminished osseointegration could be expected, which could reduce the stability of dental implants.

Many recently published studies used animal testing models. For example, there are articles in which

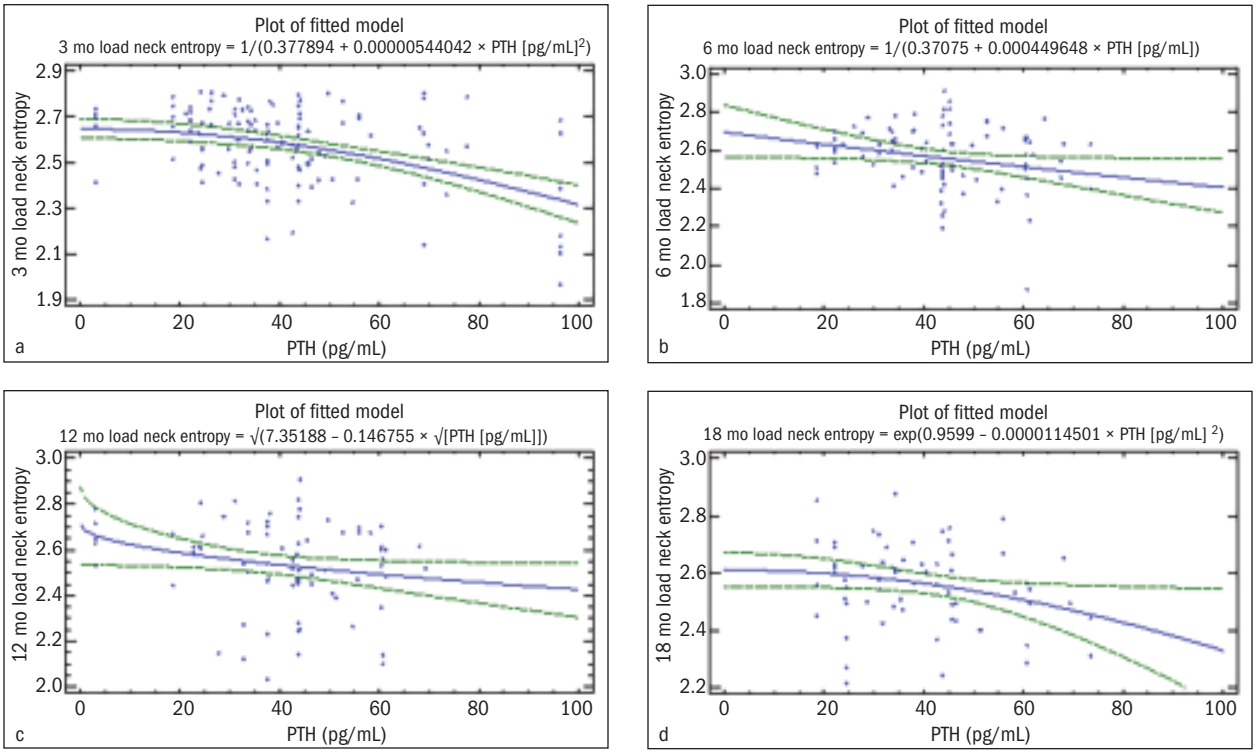

Fig 3 Relationship between parathyroid hormone and textural entropy of bone image in dental implant neck region. Simple regression of textural entropy versus parathyroid hormone: *(a)* 3 months after functional loading ($P < .05$); *(b)* 6 months after functional loading ($P < .05$); *(c)* 12 months after functional loading ($P < .05$); *(d)* 18 months after functional loading ($P < .05$).

Table 1 Relation of Parathyroid Hormone Serum Level and Bone Structure (Expressed by Value of Radiologic Entropy of Dental Implant Surrounding Bone)

Follow-up	Correlation coefficient	R^2 (%)	F ratio model	*P* value
Implantation	0.10	1.0	2.47	.1174
Immediately after functional loading	–0.06	0.4	0.72	.3972
3 mo after functional loading	0.45	19.8	31.12	.0001*
6 mo after functional loading	0.23	5.2	4.73	.0324*
9 mo after functional loading	0.25	6.1	3.55	.0648
12 mo after functional loading	–0.23	5.3	4.22	.0434*
18 mo after functional loading	–0.25	6.4	4.66	.0343*
24 mo after functional loading	–0.16	2.5	1.14	.2912

*Statistically significant ($P < .05$).

Table 2 Comparison of Location-Dependent Entropy Distribution in Intraoral Radiographs

Location	Dental implants (n)	Entropy (mean ± SD)							
			Time after functional loading						
		Implantation	Immediately	3 mo	6 mo	9 mo	12 mo	18 mo	24 mo
Maxilla									
Anterior	77	2.677 ± 0.145	2.672 ± 0.178	2.636 ± 0.204	2.631 ± 0.161	2.583 ± 0.18	2.604 ± 0.182	2.538 ± 0.163	2.529 ± 0.194
Posterior	75	2.793 ± 0.139	2.722 ± 0.179	2.634 ± 0.188	2.639 ± 0.133	2.657 ± 0.086	2.624 ± 0.224	2.608 ± 0.159	2.662 ± 0.081
Mandible									
Anterior	17	2.719 ± 0.137	2.698 ± 0.218	2.664 ± 0.106	2.652 ± 0.372	2.679 ± 0.148	2.586 ± 0.267	2.537 ± 0.133	2.641 ± 0.089
Posterior	80	2.738 ± 0.127	2.637 ± 0.146	2.571 ± 0.119	2.592 ± 0.136	2.572 ± 0.158	2.515 ± 0.178	2.589 ± 0.136	2.52 ± 0.144

the exogenous pulse of the parathyroid hormone daily dose was administered. After injection, there were observations of an intensification of osteoblast activity, an increase of collagen type I synthesis and noncollagenous protein of bone matrix, stimulation of pre-osteoblast proliferation with maturation, and acceleration of osteogenesis.[12,13]

Some authors have shown that, under the influence of parathyroid hormone, the bone trabeculae increase their thickness, volume, and mineralization.[12] Trabecular bone is the main place for bone mass growth. However, an increase of thickness in cortical bone was observed.[13,14] Also, there were sudden increases in the strength of the head and neck of the femur and the vertebrae.[15,16] The hypothesis that trabecular bone forms at the expense of cortical bone was demonstrated to be invalid.

There are studies based on critical damage of bone trabeculae that could not be restored using parathyroid hormone therapy.[17] It is suspected that thickness of the bone trabeculae increased; however, it would be impossible to restore the bone structural continuity. Although surveys showed that structural continuity could not be restored, mechanical parameters improved significantly.[6,18] Interruption of therapy resulted in reduction of those parameters.

In studies performed on rodents, very high doses of parathyroid hormone for an almost lifelong period were administered. In some of these cases, osteosarcoma developed. In similar studies performed on monkeys, no such side effects were observed.[19] Researchers have noted that human cortical bone differs from rodent cortical bone in that the first does not contain Haversian sites. That finding explains why studies on monkeys appear to be more appropriate because the structure and mechanisms of bone remodeling are notably similar to those observed in humans. They observed that parathyroid hormone administration increased the amount of connections between bone trabeculae. After 6 months from the interruption of parathyroid hormone therapy, the bone structure did not change its properties.[20]

Further studies will reveal whether higher levels of parathyroid hormone within the normal range may have an impact on implant success.

A potential aspect of parathyroid hormone activity that could lead to regeneration of bone changes due to osteoporosis as well as a decrease of bone loss in overloaded dental implants was shown. Parathyroid hormone stimulates regeneration after bone fractures and improves osseointegration of dental implants placed in preexisting bone defects.[21] Moreover, apart from periodontal treatment, parathyroid hormone enhances efficient bone formation as an adjunctive therapy in patients with acute periodontitis.[22]

The 1-34 fragment of parathyroid hormone enhanced bone healing after fracture.[22,23,24] Furthermore, in surveys based on animal testing, parathyroid hormone treatment increased bone regeneration around implants placed in earlier prepared bone. This increase could be a result of the osteogenic properties of parathyroid hormone.[22,25,26]

A synergic osteogenesis of functional loading and administration of intact parathyroid hormone (1-34 fragment) was shown.[27] Used alone, each of the single methods did not induce such processes.[22] Cooperative action of parathyroid hormone and physiologic loading on osteogenesis occur, especially in jawbones, because of the continuous forces of masticatory functions. Additionally, parathyroid hormone could be a potential factor to reverse bone loss and increase reosteointegration.[22] However, the major bone remodeling systemic regulators consist of the parathyroid hormone, calcitriol, growth hormone, thyroid hormone, glucocorticoids, and sex hormones.[28]

In a 2-year period, in rats that received noncarcinogenic doses of recombinant parathyroid hormone (1-34), an induction of osteosarcoma was observed.[29] Perhaps future studies in implantology should focus primarily on low doses and short exposures to parathyroid hormone.[30]

Pulse parathyroid hormone administration caused an anabolic osteogenesis and increased histologic osseointegration; however, an increase in the implant's primary stability was not observed.[31]

CONCLUSIONS

Assessment of the parathyroid hormone serum level could be considered as a useful method to predict bone condition around dental implants. However, one could suspect that it is not the single factor, but there are still unknown other biochemical bone condition prediction factors.

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