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Changes of procollagen type III N-terminal propeptide (PIIINP) concentrations during healing of mandible fractures treated with biodegradable and titanium fixations

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ABSTRACT

Purpose: The aims of the study were to evaluate procollagen type III N-terminal propeptide (PIIINP) concentrations in blood serum of males in the course of normal healing of mandible fractures, and to determine the correlations between kinetic changes of PIIINP, stages of fracture healing and the applied treatment.

Material and Methods: We collected blood serum samples from 43 male patients aged between 20 and 30 years, treated for mandible fractures. The patients were divided into 2 groups depending on the type of osteosynthesis used for immobilization of the fragments. Group I (n=10) consisted of patients whose reduced bone fragments were fixed with biodegradable fixations, while group II (n=33) included patients with titanium osteosynthesis devices. The control group (n=25) consisted of healthy males at the same age. PIIINP concentrations were determined with the radioimmunological method (RIA).

Results: We found a significant increase in PIIINP concentrations in both study groups (I and II) at defined stages of mandible fracture healing. Differences were noticed in the dynamics of the increase depending on the type of applied osteosynthesis devices.

Conclusion: The results point to the fact that the injury and/or mandible fracture increase the collagen type III metabolism and its dynamics depends on the type of the used bone fixation.

Key words: Procollagen type III N-terminal propeptide, bone fracture healing, biodegradable fixation, titanium fixation, osteosynthesis

INTRODUCTION

Osteosynthesis using titanium plates and screws is considered to be "the gold standard" for fixation of facial skeleton fractures [1]. Despite improved materials used to manufacture metal plates, some disadvantages are still present: rigidity, bone resorption around the implant, hypersensitivity to cold in the treated area, deformation of the face at the bone fixation site–especially in areas covered by a thin layer of tissues, metallosis, and need to remove plate and screws after clinical synostosis (especially in children due to growth disturbances and osteosynthesis device migration) [1,2].

Plates and screws made of biodegradable synthetic materials, mainly polyglycolide (PGA) or polylactide (PLA), are the alternatives for titanium osteosynthesis devices in the treatment of facial skeleton fractures**.** The biodegradable osteosynthesis materials undergo gradual total resorption, from the setting, which enables stable immobilization of bone fragments, to the clinical synostosis [2].

The disadvantage of biodegradable osteosynthesis is the need to thread drilled holes in the bone before screwing the plate, and the large size of plates and screws due to their weaker mechanical characteristics [1]. However, differences in the sizes become unimportant as the osteosynthesis techniques and biodegradable materials, used for device manufacturing (composition, polymer chains setting), gradually improve [2].

So far, the usefulness of the biodegradable plates and screws for facial osteosynthesis has been estimated on the basis of biomechanical and histomorphometric examinations in animal models and clinical examinations on the basis of subjective, objective, and radiographic studies [1-10]. In earlier studies, the usefulness of determining the metabolism of type I and III collagen markers as non-invasive and repeatable methods was established for the evaluation of the healing process [11-17].

In a mature bone, collagen type I constitutes more than 90% of the organic matrix of the bone tissue. Studies reveal [18-21], that in the course of fracture healing with immobilization of bone fragments, the regenerative tissue contains mainly collagen type I and III, with their amounts changing in time. The metabolism of human collagen type I and III can be assessed on the basis of determined products of collagen synthesis and degradation released to blood [11-17].

Procollagen type III N-terminal propeptide (PIIINP) allows for examination of collagen metabolism. It is produced during collagen synthesis in a process of enzymatic release from a precursor molecule – procollagen. Detached N-terminal propeptides are released to extracellular fluid only partially. In blood serum, only the released part of PIIINP molecules points to the synthesis of collagen type III. The rest of N-terminal propeptides is connected to newly produced fibers of collagen type III and their release takes place during collagen degradation. Thus, PIIINP present in blood serum can reflect, both, the synthesis and degradation of collagen type III, and determining PIIINP concentrations in blood serum with the radioimmunological method (RIA) enables the evaluation of the type III collagen metabolism [11,12,22-25].

MATERIAL AND METHODS

The study group consisted of 43 male patients, aged between 20-30 years, treated in the Department of Maxillofacial and Plastic Surgery of the Medical University of Bialystok (Poland) due to mandible fractures. The qualifying criteria were: the diagnosis of mandible fracture based on the clinical and radiological examinations; no skin injuries or other body injuries including other fractures; no central nervous system injuries; interview; subjective examination; basic laboratory blood and urine tests revealing no past or co-existing systemic or metabolic diseases; no history of treatment for bone fractures during last 5 years; no history of taking hormonal, anticoagulant, anticonvulsant, or diuretic drugs, preparations of calcium, magnesium, vit. D; no alcohol or narcotic drugs dependence; no alcohol consumption on the day of the accident; satisfactory clinical condition of the teeth and periodontium. The last criterion was assessed by physical and radiological examination. Satisfactory clinical condition of the teeth and periodontium was understood by proper oral health (no deep caries, no pulp gangrene and its complications, no periodontal disease, or any other oral cavity diseases). All patients have been informed of the study and have given written consent for blood collection (6 samples in appropriate intervals).

Depending on the treatment methods of the mandible fracture, the patients were divided into 2 groups: group I consisted of patients whose reduced bone fragments were fixed using biodegradable devices (n=10) and group II included patients with titanium osteosynthesis devices (n=33).

The control group consisted of healthy males, aged between 20-30 years (n=25). In group I, there were 5 patients (50%) with single mandible fracture and 5 patients (50%) with multiple mandible fractures. The most common locations for the fractures were: the angle of the mandible (43.8%), mandibular body in the canine region (25%), and mandibular body in the molar region (12.5%). In group II, single fractures of the mandible were observed in 11 patients (39.4%) and multiple fractures in 22 patients (60.6%). The fractures were most commonly located at the angle of the mandible (25%), the condyloid process (21.1%) and the molar region (17.3%).

The procedure was performed under general anesthesia with endotracheal intubation, using intraoral or extraoral incision. Bone fragments were reduced and fixed using miniplates and screws: in group I–biodegradable 2.5mm INION plates (Inion Ltd, Tampere, Finland) and in group II – titanium (Medgal, Poland).

In group I, osteosynthesis was performed on one side of the mandible in 5 patients and on both sides of the mandible also in 5 patients. In group II, osteosynthesis was performed on one side in 11 patients and on both sides in 22 patients. In order to stabilize the occlusion in both groups of patients, we used the intermaxillary immobilization with Tigerstedt's wire splints for 2 weeks after the operation. The titanium screws and plates used for osteosynthesis in group II were removed after 3 months.

Surgical procedures in both groups of patients were performed between 2nd and 5th day after trauma. Patients with the mandibular body fracture were given an antibiotic (most frequently lincomycin) for 5-7 days after the operation due to the contact of the fracture fissure with the environment of the oral cavity. Clinical and radiological evaluations, revealed no complications in the process of healing in both groups of patients; no increased periosteal reactions were observed in patients from group I. Blood samples were collected for PIIINP determination, during hospital and further ambulatory treatment, on the 2nd, 14th, 42nd, and 90th day after the injury

and on the 2nd and 14th day after the surgical procedure. We established the days of the marker determination in the course of healing based on the duration of 4 phases of healing (in the mechanism of spontaneous synostosis) and they were: the 2nd day – phase I (inflammatory), the 14th day – phase II (granulation), the 42nd day – phase III (callus, i.e. clinical synostosis), and the 90th day – phase IV (callus rebuilding) [4, 5, 7]. Blood sampling on the 2nd and 14th day after the operation was performed in order to additionally evaluate the effect of the surgical procedure and soft tissue healing on PIIINP concentration.

The blood samples were collected from the elbow vein, between 7.30 and 9.00 AM after overnight fasting for the clot to the probe. After clotting, the blood was centrifuged; aspirated serum was frozen at -80^{0}C for further PIIINP determination. The blood serum from the 25 healthy males in the control group was taken once in the same way.

The concentrations of PIIINP in blood serum were determined using ready RIA-kits (Orion Diagnostica, Finland). The results were presented as arithmetic means (X) for the two study groups and 4 stages of fracture healing, with standard deviations (SD). Statistical analysis was performed using STATISTICA 8.0. The normal distribution in trials was tested with the Shapiro-Wilk tests. Homogeneity of variance was tested with Levene's test. Sphericity of data (the equality of variances of differences between the pairs of groups) was verified with the Mauchley's test and the differences between groups I and II – with Student's t test. In order to check the differences among multiple groups, the analysis of variance (ANOVA) with repeated measurements was used. In case of sphericity assumption violation, we used Greenhouse-Geissler corrections. The post-hoc analyses were carried out with the Scheffe's test (contrasts analysis).

The study protocol was approved by the Ethics Committee of the Medical University of Bialystok (Poland).

RESULTS

Statistical analysis of patient subgroups, with single and multiple mandible fractures, did not show any differences. However, we found the differences related to the kind of fracture immobilization methods. Thus, the results were presented in two groups.

Group I

In blood serum of patients treated with biodegradable osteosynthesis, in the course of mandible fractures healing, the increase in PIIINP concentrations on all examination days was observed as compared to the controls. The dynamics of the increase in this propeptide concentration was as follows: on the 2nd and 14th day after the operation and on the 14th and 42nd day after the injury the PIIINP concentrations were similar. The highest propeptide concentration was observed on the 90th day after the injury (*Fig. 1*).

In comparison to PIIINP concentrations of the controls, an increase in propeptide concentration in all examined periods of fracture healing in patients from group I was statistically significant ($p<0.001$) (*Tab. 1*). The statistically significant differences were obtained by comparing PIIINP concentrations between the 2nd and 90th day (*Tab. 2*).

Group II

Similarly to group I, we found an increase in PIIINP concentration on each day of the healing in patients with mandible fracture treated with titanium osteosynthesis as compared to the controls. Propeptide concentrations on the 2nd, 14th, 42nd, and 90th day after the injury were very similar. The highest increase in PIIINP concentration was observed on the 2nd and 14th day after the operation. The concentrations were found on the similar level (*Fig.1*).

The increase in propeptide concentrations observed on particular days of mandible fracture healing after the injury and operation was statistically significant ($p<0.001$) in relation to PIIINP concentrations in the control group (*Tab. 1*).

Statistically significant differences of PIIINP concentrations between days after the injury and after the operation are presented in *Tab. 3*.

The changes of PIIINP concentrations in time depend significantly ($p<0.001$) on the treatment method used (*Tab. 1* and *Fig. 1*). The dynamics in particular study groups is completely different. PIIINP concentrations in each study group show a growth tendency. However, the increase was higher in group I and the difference between groups changed on particular days of evaluation. On the 2nd day after the injury and the 2nd day after the operation, no statistically significant difference was noted. However, the difference became statistically significant with time as the fractures were healing, i.e. on the 12th, 42nd, and 90th day after the injury (*Tab. 1*).

Figure 1. **PIIINP serum concentrations in patients of both groups on days of healing and in control group (C).**

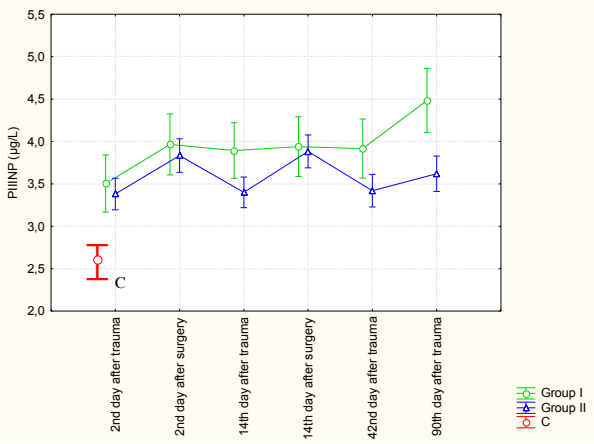

Table 1. **PIIINP serum concentrations in patients of both groups and in control group (C) on particular days after injury and after operation.**

	2nd day after trauma	2nd day after surgery	14th day after trauma	14th day after surgery	42nd day after trauma	90th day after trauma
Group I Mean concentration of PIIINP ±SD (μg/L)	* 3.50±0.75	* 3.97±0.76	* 3.89±0.54	* 3.94±0.64	* 3.91±0.84	* 4.48±1.06
Group II Mean concentration of PIIINP ±SD (μg/L)	** 3.38±0.44 NS	** 3.83±0.56 NS	** 3.40±0.49 ^	** 3.88±0.53 NS	** 3.42±0.44 ^^	** 3.62±0.43 ^^^
Control group (C) Mean concentration of PIIINP ±SD (μg/L)	2.66 ± 0.55					

** p<0.001 - significance level (p) between group I and the control group (C)*
*** p<0.001 - significance level (p) between group II and the control group (C)*
NS – no statistical significance between group I and group II
^ p=0.009; ^^ p=0.017; ^^^ p<0.001 - significance level (p) between group I and group II

Table 2. **Statistical differences between PIIINP serum concentrations on particular days of examination in group I (NS – statistically non-significant).**

	2nd day after trauma	2nd day after surgery	14th day after trauma	14th day after surgery	42nd day after trauma	90th day after trauma
2nd day after trauma		NS	NS	NS	NS	p<0.001
2nd day after surgery	NS		NS	NS	NS	NS
14th day after trauma	NS	NS		NS	NS	NS
14th day after surgery	NS	NS	NS		NS	NS
42nd day after trauma	NS	NS	NS	NS		NS
90th day after trauma	p<0.001	NS	NS	NS	NS	

Table 3. **Statistical differences between PIIINP serum concentrations on particular days of examination in group II (NS – statistically non-significant).**

	2nd day after trauma	2nd day after surgery	14th day after trauma	14th day after surgery	42nd day after trauma	90th day after trauma
2nd day after trauma		p<0.001	NS	p<0.001	NS	p<0.001
2nd day after surgery	p<0.001		p<0.001	NS	p<0.001	p<0.001
14th day after trauma	NS	p<0.001		p<0.001	NS	p<0.001
14th day after surgery	p<0.001	NS	p<0.001		p<0.001	p<0.001
42nd day after trauma	NS	p<0.001	NS	p<0.001		p<0.001
90th day after trauma	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	

DISCUSSION

Osteosynthesis with titanium plates and screws is the basic surgical method of treatment of the facial bones fractures. This method fulfills the requirements of nowadays therapy, as it enables to obtain a permanent and functional osteosynthesis of bone fragments. However, because of the harmful effect of the titanium plates they are presently replaced by biodegradable plates and screws. Such osteosynthesis gives the opportunity for gradual transfer of the physiological load onto bone tissue in the period of healing. It has a significant meaning in the mechanism of restoration of bone continuity after the fracture. The obstacle in their common use is obtaining appropriate durability of the biodegradable miniplates and screws for a period necessary for clinical synostosis, especially in the mandible exposed to significant physiological load [1-10].

Collagen is the main organic component of a mature bone enhancing its durability under load. It is assumed, that the intensity of synthesis of various types of collagen, mainly of types I and III, is one of the basic measures of bone recovery processes [18-21,26]. In our study, the evaluation of PIIINP concentrations was conducted in serum of male

patients during the course of fracture healing with the use of biodegradable or titanium plates and screws.

In the blood serum of males from both study groups, we observed a significant increase in PIIINP concentrations in all stages of fracture healing. The difference in the dynamics of the increase was found by analyzing PIIINP concentrations in both groups of patients on particular days after the injury. In the group of patients treated with biodegradable osteosynthesis (group I), the values of PIIINP concentrations on the 14th and 42nd day after the injury and 2nd and 14th day after the operation were similar, however, on the 90th day after the injury the values showed a considerable increase.

In patients from group II, the increase in PIIINP concentrations remained on a quite stable level after the injury although with a slight but permanent growth tendency. A slight increase in PIIINP concentrations in this group was noticed only on the 2nd and 14th day after the operation.

The results may suggest, that the injury and/or the course of fracture healing affect the increase in type III collagen metabolism, and its kinetics depends on the method of treatment.

Considering the differences in duration of healing of mandible fractures and particular long bones, similar results regarding group I (treated with biodegradable plates) were obtained by Joerring et al. [14] in the course of normal healing of the forearm fractures treated with the preservative-orthopedic method. The authors found a significant increase in PIIINP concentrations in all stages of the study, i.e. in the 1st, 2nd and 5th week and in the 9th month after the injury. Kurdy et al. [16] showed very similar, to our results, dynamics of the increase in PIIINP concentrations in blood serum of patients in the normal healing of tibia fractures treated with the preservative-orthopedic methods. They observed a statistically significant increase of propeptide concentrations between the 1st day after the injury and consequent stages of their study i.e. from the 8th day to the 5th week. The increase in PIIINP concentrations in the 5th week remained on a similar level in the 10th, 14th and 20th week after the injury [17]. The results of the studies discussed above [16,17] seem to confirm our conclusions.

Veitch et al. [27] evaluated PIIINP concentrations in patients with tibial shaft fractures treated with the preservative-orthopedic and operative methods. The authors found a statistically significant increase in PIIINP concentrations throughout the whole period of study, i.e. from the 2nd to the 168th day after the injury. In contrast to our earlier [11,12] and present studies, they did not show any differences in the dynamics of PIIINP concentrations related to the method of treatment [27].

Similarly, Joerring et al. [15] in the normal healing of the tibia fracture treated with the preservative-orthopedic and surgical methods observed a statistically significant increase in PIIINP concentrations in the 1st and 2nd week after the injury. Further observations of the study, revealed that the propeptide concentrations were elevated till the end of the study, i.e. 26th week after the injury. The authors did not show any differences in the dynamics of PIIINP concentration changes related to the type of fracture and method of treatment [15].

The discrepancies can be due to the fact that the results of PIIINP concentrations were compared to the 1st day after the injury and not to the controls, and related to the type of fractured bones [11,12,15,27,28].

Stoffel et al. [29], for 24 weeks, evaluated PIIINP concentrations in patients in the course of healing of the bones of the lower extremities (group I) and closed fractures of the distal end of the fibula (group II) treated with plate osteosynthesis. The authors observed an increase in PIIINP concentrations after the operation, in both groups, in comparison to the concentration of the marker on the 1st day of the study. The maximum concentrations of marker of the type III collagen metabolism in group I were observed in the 2nd week, while in group II in the 12th week after the operation. The values of PIIINP concentrations were found to return to their initial level in group I after 6 weeks and in group II between the 12th and 24th week after the operation. Based on their results, the authors assumed that the duration of fracture healing and the range of PIIINP concentration changes are related to the size of the fracture [29].

The results of the earlier studies [11,12,14-17,27-29] seem to confirm our conclusion, that the course of normal healing of the mandible fractures can influence the increase of the type III collagen metabolism.

Our studies, did not show statistically significant differences in PIIINP concentrations between the subgroups with single and multiple fractures of the mandible. However, comparing the mean concentrations of PIIINP, obtained on particular days of the study in groups I and II, we observed a statistically significant difference in the dynamics of PIIINP concentrations related to time of fracture healing. This result suggests, that the type of used osteosynthesis can influence this difference. Strength and stiffness of the bone fragments fixed with the biodegradable miniplates is lower than in the titanium osteosynthesis device. It may point to various mechanisms of bone continuity restoration depending on the used osteosynthesis devices: in group I (biodegradable osteosynthesis) by spontaneous synostosis and in group II (titanium osteosynthesis) by primary and/or indirect synostosis [11,12,30,31]. However, it requires further investigation with a larger group of patients and for a longer period of time.

Joerring et al. [15] and Kurdy et al. [17] determined PIIINP concentrations in blood serum in single cases of patients with delayed synostosis of the tibia. They claimed, that propeptide concentrations in these patients were statistically significantly higher than in those with normal course of fracture healing. Based on the results, they concluded about the usefulness of PIIINP concentration determination as a non-invasive

method for the evaluation of normal and abnormal course of fracture healing in humans [15,17].

Seebeck et al. [32] in a 63-day evaluation of experimental healing of the fibular shaft fracture in sheep with a 3mm bone defect at the site of the fracture fissure, treated with an external stabilizer, found a decrease in PIIINP concentrations up to the 5th week after the procedure, an increase between the 5th and 6th week and afterwards a decrease to the initial values. Klein et al. [33] in a similar study on healing of tibia fractures in sheep, found an increase in PIIINP concentrations in the 2nd, 6th, and 8th week after the operation. However, in sheep treated with intramedullary osteosynthesis the authors observed a decrease in PIIINP concentrations during the 9 weeks stage of healing [33]. In contrast to our earlier studies and studies by other authors [11,12,14,16], both Seebeck et al. [32] and Klein et al. [33] suggested the usefulness of PIIINP for the evaluation of degradation processes rather than for the callus formation.

In the course of long bone fracture healing in animals, collagen type III appears early and in greater amounts than collagen type I [21,26]. In the granulation phase, Phill et al. [21] and Ashhurst et al. [26] observed greater amount of collagen type III in loose connective tissue filling the space between bone fragments, in the region of blood vessels formation and in the connective tissue forming on the periphery of periosteum. Significant amounts of collagen type III and type I were observed in the callus, forming between the bone fragments. In contrast, in the periosteal callus, the authors observed mainly collagen type III which remained dominant to collagen type I till the end of the study, i.e. till the 4th week [21,26].

The role of collagen type III during fracture healing has not been fully explained. It is assumed, that collagen type III may play a role of „a limited framework" that enables migration, bone cells adhesion and in-growing of blood vessels [21, 26].

In our study, the statistically significant ($p<0.001$) increase in PIIINP concentrations, found 2 days after the injury, can be a generalized reaction to the injury from, both, the skeletal system and soft tissue. Our results are consistent with a study by Waydhas et al. [34]. They observed a significant increase in PIIINP concentrations in blood serum of patients with severe body injuries between the 3rd and 14th day after the injury. Additionally, the authors point to the fact that PIIINP concentrations were considerable higher in patients with co-existing bone fractures [34].

Considering the order of appearance of collagen type III and I in animal models of fractures, the concentrations of PIIINP on the 14th day of our study may be the result of collagen type III synthesis. In this stage of mandible fracture healing, fibroblast-like cells, that form the loose connective tissue, can be the source of synthesis of collagen type III [20,21,26]. Since only collagen type I is a substrate in the process of mineralization in the bone organic matrix [21,35], high PIIINP concentration observed on the 42nd day, i.e. in the stage of clinical mandible synostosis, may be the result of degradation of previously synthesized collagen type III. A study by Wen et al. [35], showed the necessity of collagen type III replacement with collagen type I in the stage of bone fracture healing. The study showed, that the lack of replacement of collagen type III with collagen type I was the reason for bone synostosis disorders. It led to insufficient mineralization of newly formed bone tissue [35].

Multimaki et al. [20] showed that the highest level of mRNA for collagen type I could be observed in the phase of callus rebuilding and lamellar bone formation. In this phase of healing, the level of mRNA for collagen type III was minimal. Taking into account this data, it could be assumed, that high PIIINP concentrations revealed on the 90th day after the mandibular fracture are the result of collagen type III degradation. It also shows, that the process of fracture healing is in progress. The differences of PIIINP concentrations determined in both of our study groups, in the course of normal mandible fracture healing, may suggest a decreased stabilization of bone fragments in group I due to biodegradation of osteosynthesis devices which enables micro-movements of bone fragments and thus, leads to faster rebuilding of formed callus in the fissure of the fracture [1,2,7].

Apart from bone fracture healing, collagen type III is synthesized as the first substance during the restoration of soft tissues [22,23]. It is assumed, that collagen type III is an important constituent of the majority of systemic restoration processes [21,23-25,34]. However, studies by Haukipuro et al. [22,23] showed that only extensive surgical procedures of the abdominal cavity influence the changes of PIIINP concentrations in blood serum. On the contrary, in the course of healing of small soft tissue injuries, e.g. after a surgical repair of abdominal hernia, there were no changes in this propeptide concentrations in blood serum [22,23].

In the present study, patients in both groups had either closed fractures of the mandible or open mandible fractures with contact with the oral cavity environment through the gingival wound, seldom through the mucous membrane wound or through the periodontal space. In accordance with the rules of the maxillofacial and plastic surgery the surgical incisions of the soft tissue of the face were very spare. Additionally, in order to evaluate the effect of soft tissue healing on PIIINP concentrations in the blood serum of patients after surgical treatment, 2 additional determinations of propeptide were introduced: on the 2nd and 14th day after the surgery. The values of PIIINP concentrations obtained on these days, as well as the data from the available literature, showed that the influence of soft tissue healing on PIIINP concentrations in our study was not significant.

Explanation is also required regarding the difference in the number of patients in group I and II. It is related to the limited financial capacity of the project and the high costs of biodegradable fixation that are not normally used in the

treatment of facial bone fractures. However, due to the clinical importance, further research is necessary.

CONCLUSIONS

Statistically significant increase in PIIINP concentrations in the blood serum of males, observed in various stages of the normal course of mandible fracture healing, points to the fact, that the injury and /or healing course increase the metabolism of collagen type III. Differences in the dynamics of PIIINP concentrations in patients of group I and II may suggest various mechanisms of mandible fracture healing depending on the type of the used fixations.

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