International Journal of Medical Sciences And Clinical Research

VOLUME Vol.05 Issue05 2025
PAGE NO. 88-91
DOI 10.37547/ijmscr/Volume05Issue05-18

# The Prognostic Value of Markers of Bone Metabolism

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**Received:** 31 March 2025; **Accepted:** 29 April 2025; **Published:** 31 May 2025

**Abstract:** Biomarkers of bone metabolism, including biomarkers of bone collagen, have attracted great scientific interest. Numerous international studies indicate the importance of these markers in assessing the degree of bone tissue damage, which have not only diagnostic but also prognostic value.

**Keywords:** Biomarkers of bone metabolism, bone tissue, acute hematogenous osteomyelitis, collagen.

**Introduction:** Today, acute hematogenous osteomyelitis (CGO) remains a serious problem in childhood. According to WHO, the annual incidence of acute respiratory viral infections among children ranges from 2 to 13 cases per 100,000 population, depending on the region, age and quality of medical care. In developed countries such as the USA, Canada and Western European countries, the incidence of osteomyelitis in children remains relatively stable – about 5-7 cases per 100,000 children per year. However, in Africa, South Asia, and Latin America, the incidence of CSOs is significantly higher, reaching 15-20 cases per 100,000 children. In addition, numerous studies indicate an increase in the incidence of osteomyelitis, which is associated with the growth of antibiotic–resistant bacterial strains (for example, MRSA - methicillin-resistant Staphylococcus aureus), as well as insufficient vaccination against hemolytic streptococcus and pneumococcus, a high incidence of injuries among children, limited access to medical care and untimely treatment of bacterial infections, high survival newborn children with immunodeficiency due to the development of neonatology.

**The purpose of the study**

In this regard, the purpose of our study was to study biomarkers of bone metabolism, namely type I procollagen aminotherminal propeptide (PINP) and type I collagen carboxytherminal telopeptide (β-CrossLabs) in children with acute hematogenous osteomyelitis.

**METHODS**

The study was conducted at the Samarkand State Medical University, a children's multidisciplinary surgical hospital. For the

study, we took 60 sick children, who were divided into 6 groups. Group 1 included sick children aged 0-28 days, group 2: 1-11 months, group 3: 1-4 years, group 4: 5-9 years, group 5: 10-14 years, and group 6: 15-19 years. Children from the control group were assigned to each study group. Concentrations of type I procollagen aminotherminal propeptide (PINP) and type I collagen carboxytherminal telopeptide (β-CrossLabs), as well as levels of calcium, phosphorus, and alkaline phosphatase were studied in all children. These indicators were determined on the 1st day of admission, on the 7th day after surgical treatment, and in the long-term period after treatment (after 6 months). To study these indicators, methods of enzyme immunoassay and biochemical analysis were carried out.

**RESULTS AND DISCUSSION**

Bone tissue is a highly specialized metabolically active mineralized connective tissue. Its structural and functional integrity is ensured by two multidirectional processes, such as the formation and resorption of bone tissue, the intensity of which is determined by the activity of the cellular elements of bone, that is, osteoblasts, osteoclasts and osteocytes. Osteoblasts are responsible for formation, osteoclasts for resorption, osteocytes for maintaining the structural and functional activity of mature bone tissue. The most important biopolymer of bone tissue is protein, type 1 collagen, which makes up more than 90% of the

mass of the organic bone matrix, which plays a key role in the mineralization of the intercellular matrix of bone tissue, as well as in ensuring the strength properties of bone.

Thus, the metabolic state of the main bone protein, collagen, is determined by the intensity and direction of its synthetic or, conversely, catabolic processes. This indicates that shifts in bone collagen metabolism directly reflect the general trend of metabolic processes in bone tissue. The balance between the synthesis and breakdown of bone collagen is a complex multi-stage process involving both extracellular and intracellular stages. The levels of bone formation or bone breakdown can be assessed by analyzing the components of bone collagen released into the blood. Thus, markers of type 1 collagen synthesis include the amino terminal propeptide procollagen type 1 (PINP – from English N-terminal propeptide of type 1 collagen). Under the action of catabolic factors, mainly osteoclasts, amino- and carboxytherminal telopeptides, called N-terminal (NTX-1) and C-terminal telopeptides (CTX-1), are cleaved from the type 1 collagen molecule. In this case, CTX -1 can have 2 forms: alpha- CTX and beta- CTX. Beta – CTX contains beta-isomerized aspartic acid (beta-CrossLaps, from the English beta- isomerized carboxy-terminal cross-linking region of collagen type 1). It is a beta-isomerized carboxytherminal fragment of a type 1 collagen molecule, which is a specific marker of bone resorption.

Bone tissue in young children contains less collagen and more non-collagen proteins, and is also rich in glycosaminoglycans. The majority of collagen in children is soluble, poorly resistant to heat and the action of collagenolytic enzymes; at the same time, biosynthesis proceeds at a high rate. With age, the relationship of collagen with non–collagen proteins increases - proteoglycans, glycoproteins, phosphoproteins. As a result, the solubility of collagen decreases, the mechanical strength of collagen fibers increases, resistance to denaturing factors and collagenase; the mineral component of bone increases significantly. As a result of the implementation of the above–mentioned mechanisms, a pronounced anabolic effect in the exchange of bone collagen is manifested, which may explain the increase in the concentration of the bone formation marker P1NP on all days of observation after surgery, especially in the group of young and middle-aged children.

In the first group of children (0-28 days old), the level of the marker of bone collagen resorption before surgery and on the 7th day after surgery practically did not differ from the data of the control group (1,115 ng/ml) and amounted to 1,144 ng/ml (P>0.05) and 1,232 ng/ml (P>0.05), respectively. 6 months after surgery, the content of ?-CrossLaps in blood serum increased by 119.3% compared with the control group and amounted to 2.446 ng/ml (P=0.001). The amount of type I collagen formation marker in bone tissue increased significantly before surgery, on day 7 after surgery, and after 6 months of follow-up, respectively, from 6.31 ng/ml (in the control) to 9.58 ng/ml (P=0.012), 10.25 ng/ml (P=0.012), and 15.77 ng/ml (p=0.001), respectively.

The results of the studied indicators in the 2nd group of children (1-11 months) indicate an increase in both resorption markers and markers of type I collagen formation in the blood serum. Thus, the content of ?-CrossLaps was increased both before surgery (by 110.2%; P=0.002) and on days 7 and 60 after surgery by 275.7% (P=0.001), respectively. Noteworthy is the significant increase in the studied indicator from 0.766 ng/ml (in the control) to 2.878 ng/ml (P=0.001) on the 7th day after surgery.

The concentration of the N-terminal propeptide procollagen type I (PINP) during these observation periods also increased by 117.4% (P=0.003), 152.5% (P=0.001) and 123.8% (P=0.001), respectively. In the group of children aged 1 to 4 years, there was a maximum increase in the concentration of BNP in the blood serum both before surgery and on the 7th day after surgery. During these periods, the level of the analyzed indicator increased by 11.4 and 9.2 times, respectively, compared with the control group. At the same time, the content of ?-CrossLaps increased, although not as pronounced. Thus, the concentration of the marker of bone collagen resorption increased from 0.86 ng/ml (in the control) to 1.413 ng/ml (P=0.001) before surgery and 1.617 ng/ml (P=0.001) on day 7 after surgery. Similarly to the changes in bone collagen metabolism in group 3, there were shifts in the content of the studied markers in children aged 5 to 9 years in the first 7 days of observation.

Thus, the level of procollagen type I N-terminal propeptide (PINP) was increased before surgery from 2.89 ng/ml (in the control) to 16.95 ng/ml (P=0.001). On day 7 after surgery, PINP decreased slightly to 12.62 ng/ml, but was 4.5 times higher than the control values (P=0.001). 6 months after surgery, the studied marker remained significantly elevated and amounted to 22.76 ng/ml (P=0.001). The content of ?-CrossLaps in the analyzed group before surgery did not differ from the control, increased by 44.6% (P=0.021) on the 7th day after surgery and increased significantly by more than 5 times on the 6th month of follow-up. A distinctive feature of type I bone collagen metabolism in group 4 was a significant increase in the concentration of markers of both osteogenesis and its resorption in the long-term period after surgery. At the same time, the

PINP content increased more significantly than the level of -CrossLaps, which indicates an increase in synthetic processes over its breakdown in bone collagen metabolism.

In the group of children aged 10 to 14 years, the level of the marker of bone collagen formation PINP increased over time. Thus, before surgery, the PINP content was increased by 3.74 times (P=0.001) compared with the control group; after surgery, on day 7, it increased by 4.78 times (P=0.001), and after 6 months – by 5.59 times (P=0.001). The amount of the bone resorption marker -CrossLaps varied in phases: it was increased by 24.5% (P=0.036) before surgery, did not differ from the data of the control group a week after surgery, and increased again by 49.5% (P=0.001) after 6 months of follow-up.

The opposite changes, in contrast to the shifts in group 5, were noted in the indicators of type I collagen metabolism in children aged 15-19 years, where there was a significant increase in -CrossLaps, a marker of bone resorption, both before surgery and in the dynamics of observations after surgery. Thus, the content of the studied marker before surgery was increased by 59.8% (P=0.002) compared with the control; 3.9 times on the 7th day after surgery (P=0.001), 10.5 times after 6 months (P=0.001). At the same time, the increase in PINP in the dynamics of observations was not so significant: before surgery, it increased from 11.60 ng/ml (in the control) to 13.46 ng/ml (P>0.05), on the 7th day after surgery to 15.02 ng/ml (P=0.001) and after 6 months to 16.59 ng/ml (P=0.002). Thus, the dynamics of changes in the content of markers of bone collagen metabolism in the blood serum of children aged 15 to 19 years indicates a pronounced resorption of type I collagen both in the initial stages after surgery and in the long term.

In addition to bone biomarkers (PINP and -CrossLaps), we also studied the content of calcium, phosphorus and alkaline phosphatase, since these biochemical parameters also reflect bone metabolism and have not only diagnostic value, but recent studies indicate their prognostic value, since together with the main bone markers they can predict the outcome of the disease.

In group 1, the calcium level on day 1 was 1.81 mmol/L, followed by a moderate increase by day 7 (1.91 mmol/L) and a further increase by month 6-7 (1.98 mmol/l). Despite the statistically insignificant difference between the 1st and 7th days ($p > 0.05$), the tendency to increase calcium levels by the 6th-7th month may indicate a positive dynamics of the inflammatory process. In children of group 2 (1-11 months), the initial calcium level was 1.93 mmol/l, slightly higher than in newborns, and significantly ($p < 0.05$) increases by day 7 (1.99 mmol/l). The maximum value (2.05 mmol/l) is recorded by the 6th-7th month, which, while improving the clinical picture, indicates a favorable prognosis.

In the age group of 1-4 years and 5-9 years, the increase in Ca from day 1 to day 7 (1.97 → 1.99 mmol/l and 1.90 → 1.96 mmol/l, respectively) is small and does not always reach statistical significance ($p = 0.06$ for 1-4 years, $p = 0.08$ for 5-9 years). However, a further increase by the 6th-7th month (to an average of 2.2 and 2.0 mmol/l, respectively) correlates with an improvement in radiological and clinical parameters ($p < 0.05$). A moderate increase in calcium on the background of adequate antibacterial therapy may reflect a decrease in the activity of the inflammatory process and the restoration of bone metabolism, especially if other biochemical markers (alkaline phosphatase, phosphorus) are normalized in parallel.

In the 10-14-year-old group, the intake calcium level (2.43 mmol/L) is the highest among all ages, while by day 7 it decreases to 2.03 mmol/l ($p < 0.05$), and by month 6-7 it increases again to about 2.2 mmol/L. A sharp decrease in the acute period may indicate an intense inflammatory process and metabolic restructuring of bone tissue. In the age group of 15-19 years, initially (2.25 mmol/l) there was a slightly increased calcium, which decreased to 1.93 mmol/l by day 7 ($p = 0.04$). The increase by 6-7 months (2.05 mmol/l) indicates the restoration of mineral balance. The practical significance lies in the fact that maintaining low calcium values for longer than 2-3 weeks may signal a prolonged course of inflammation, the formation of sequestration, or insufficient effectiveness of therapy. Thus, in patients with acute osteomyelitis, the dynamics of total calcium during the acute period and the rehabilitation period can serve as an additional criterion for predicting the outcome of the disease. An increase in the indicator by the 6th-7th month, especially in combination with a decrease in the level of inflammatory markers, is considered a sign of a favorable outcome and effective therapy. In turn, insufficient growth or repeated decrease in calcium should alert the doctor and encourage an expanded diagnostic search (X-ray, MRI) and, if necessary, correction of therapeutic measures.

## CONCLUSIONS

Thus, we can conclude that the determination of markers of type I bone collagen metabolism is the most informative for assessing bone resorption, formation and regeneration, which can be used not only in the diagnosis of acute kidney injury, but also in monitoring treatment, as well as predicting the outcome of the disease.

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