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THE ROLE OF BIOCHEMICAL MARKERS IN BONE METABOLISM IN CHILDREN AND ADOLESCENTS. LITERATURE REVIEW

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Abstract

Background. Skeletal health is of paramount importance during childhood and adolescence, as it directly influences growth, development, and overall quality of life. Individuals who do not achieve optimal bone mass during these critical periods are at risk of developing osteoporosis, even if they do not experience accelerated bone loss in adulthood.

In recent years, biochemical markers have become valuable tools for assessing bone metabolism and turnover. However, interpreting these results remains challenging, as measurements fluctuate based on factors such as age, pubertal stage, growth rate, mineral accumulation, hormonal regulation, nutritional status, circadian and diurnal variations, tissue specificity, and the sensitivity and specificity of analytical methods. Serum markers of bone formation include bone-specific alkaline phosphatase, osteocalcin, and the C- and N-terminal propeptides of type I collagen. Urinary markers of bone resorption include degradation products of type I collagen such as pyridinoline (PYD), deoxypyridinoline (D-PYD), and the C- and N-terminal telopeptides of type I collagen (CTX and NTX).Therefore, it is essential to establish reference values that account for age and sex in each pediatric population, considering their specific climatic conditions and lifestyle factors.

Aim. To analyze the literature on the role of bone turnover markers and their reference values in children.

Search Strategy: A systematic search was conducted in the PubMed and Google Scholar databases using the following keywords: "bone metabolism markers," "osteopenic syndrome in children," "osteoporosis diagnosis," "C-terminal telopeptide," and "reference values of bone metabolism markers." The search was limited to studies published in English over the past 10 years. 40 sources were reviewed.

Discussion. An analysis of the literature indicates that quantitative values of osteocalcin, C-terminal telopeptide of type I collagen, N-terminal propeptide of type I procollagen, and alkaline phosphatase in the blood of healthy children and adolescents from different countries vary considerably and exhibit gender-specific differences.

Conclusion. A review of the literature underscores the importance of assessing bone metabolism markers in pediatric populations. Age-specific reference intervals for these markers, taking into account ethnic, gender, and geographic variations, are clinically significant for evaluating bone metabolism in children and adolescents.

Keywords: *"bone metabolism markers", "osteopenic syndrome in children", "osteoporosis diagnosis", "C-terminal telopeptide", "reference values of bone metabolism markers".*

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Резюме

РОЛЬ БИОХИМИЧЕСКИХ МАРКЕРОВ В КОСТНОМ ОБМЕНЕ У ДЕТЕЙ И ПОДРОСТКОВ. ОБЗОР ЛИТЕРАТУРЫ.

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Введение. Здоровье скелета имеет первостепенное значение в детском и подростковом возрасте, поскольку оно напрямую влияет на рост, развитие и общее качество жизни. Люди, которые не достигают адекватной костной массы в детстве и подростковом возрасте, подвержены риску развития остеопороза, даже если у них не происходит ускоренной потери костной массы во взрослом возрасте. В последние годы биохимические маркеры стали ценным инструментом для оценки костного метаболизма и костного обмена. Однако интерпретация результатов затруднена, поскольку такие измерения колеблются в зависимости от возраста, стадии полового созревания, скорости роста, накопления минералов, гормональной регуляции, статуса питания, циркадных колебаний, суточных колебаний и специфичности костной ткани, а также чувствительности и специфичности анализов. Сывороточные маркеры формирования костной ткани включают костную щелочную фосфатазу, остеокальцин и С- и N-концевые пропептиды коллагена I типа. Маркеры резорбции кости в моче включают продукты распада коллагена I типа, такие как пиридиновые сшивки (пиридинолин [PYR], дезоксипиридинолин [D-PYR]) и С- и N-телопептиды коллагена I типа (CTx и NTx). Таким образом, для каждой детской популяции, проживающей в определенном климате и с похожим образом жизни, должны быть получены референсные значения с учетом возраста и пола.

Цель. Анализ литературных источников о роли маркеров костного обмена и их референсных значении у детей.

Стратегия поиска. Проведен систематический поиск в базах PubMed, Google Scolar по ключевым словам: «маркеры костного метаболизма», «остеопенический синдром у детей», «диагностика остеопороза», «С концевой телопептид», «референсные значения маркеров костного метаболизма». Этот поиск был ограничен англоязычными исследованиями, опубликованными с 2015 по 2024 гг. Изучено 40 источников.

Обсуждение. Анализ публикаций показал, что количественные значения гормона остеокальцина, С-концевого телопептида коллагена I типа, N-концевого пропептида проколлагена типа I и щелочной фосфатазы в крови у здоровых детей и подростков из разных стран имели неравнозначные значения и гендерные различия.

Выводы. Анализ литературных источников показывает важность определения маркеров костного метаболизма у детей и подростков. Возрастные интервалы этих маркеров в детской популяции с учетом этнического, гендерного и географического распределения клинически значимы при оценке костного метаболизма.

Ключевые слова: *«маркеры костного метаболизма», «остеопенический синдром у детей», «диагностика остеопороза», «С концевой телопептид», «референсные значения маркеров костного метаболизма».*

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Түйіндеме

БАЛАЛАР МЕН ЖАСӨСПІРІМДЕРДЕГІ СҮЙЕК АЛМАСУЫНДАҒЫ БИОХИМИЯЛЫҚ МАРКЕРЛАРДЫҢ РӨЛІ. ӘДЕБИЕТТІК ШОЛУ.

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Кіріспе. Қаңқа саулығы балалық және жасөспірімдік шақта өте маңызды, өйткені ол өсуге, дамуға және жалпы өмір сапасына тікелей әсер етеді. Балалық және жасөспірім кезінде сүйек массасына жете алмайтын адамдарда остеопороздың даму қаупі бар, тіпті егер олар ересек жаста сүйек массасының жоғалуын тездетпесе де. Соңғы жылдары биохимиялық маркерлер сүйек метаболизмі мен сүйек алмасуын бағалаудың құнды құралына айналды. Дегенмен, нәтижелерді түсіндіру қиын, өйткені мұндай өлшемдер жасына, жыныстық жетілу кезеңіне, өсу жылдамдығына, минералдардың жиналуына, гормоналды реттеуге, тамақтану күйіне, циркадттық ауытқуларға, күнделікті өзгерістерге және сүйек ерекшелігіне, сондай-ақ талдаулардың сезімталдығы мен ерекшелігіне байланысты өзгереді. Сүйек түзілуінің сарысулық маркерлеріне сүйек сілтілі фосфатаза, остеокальцин және С - және N-терминал коллаген I типті пропептидтер жатады. Зәрдегі сүйек резорбциясының маркерлеріне пиридиндік айқаспалы байланыстар (пиридинолин [PYR], дезоксипиридинолин [D-PYR]) және I типті коллаген С - және N-телопептидтер (CTx және NTx) сияқты I типті коллагеннің ыдырау өнімдері жатады. Осылайша, белгілі бір климатта өмір сүретін және өмір салты ұқсас әрбір балалар популяциясы үшін жас пен жынысты ескере отырып, референстік мәндер алынуы керек.

Мақсаты. Сүйек алмасу маркерлерінің рөлі және олардың балалардағы референстік мәні туралы әдеби дереккөздерді талдау.

Іздеу стратегиясы. PubMed, Google Scolar деректер қорында "сүйек метаболизмінің маркерлері", "балалардағы остеопениялық синдром", "остеопороз диагностикасы", "телопептид ұшы", "сүйек метаболизмінің маркерлерінің

анықтамалық мәндері" түйін сөздері бойынша жүйелі іздеу жүргізілді. Ізденіс 2015 жылдан 2024 жылға дейін жарияланған шет тіліндегі зерттеулермен шектелді. 40 дереккөз зерттелді.

Талқылау. Жарияланымдарды талдау әр түрлі елдердің дені сау балалары мен жасөспірімдеріндегі остеокальцин, I типті коллагеннің С-терминалды телопептидінің, проколлагеннің I типті N-терминалды пропептидінің және қандағы сілтілі фосфатазаның сандық мәндері бірдей емес мәндер мен гендерлік айырмашылықтарға ие екенін көрсетті.

Қорытынды. Әдеби дереккөздерді талдау балалар мен жасөспірімдердегі сүйек метаболизмінің маркерлерін анықтаудың маңыздылығын көрсетеді. Этникалық, гендерлік және географиялық таралуын ескере отырып, балалар популяциясындағы осы маркерлердің жас аралықтары сүйек метаболизмін бағалауда клиникалық маңызды.

Түйінді сөздер: *"сүйек метаболизмінің маркерлері", "балалардағы остеопениялық синдром", "остеопороз диагностикасы", "телопептид ұшы", "сүйек метаболизмінің маркерлерінің анықтамалық мәндері".*

Дәйексөз үшін: *Мадиева М., Каскабаева А., Рымбаева Т., Канапиянова Г., Берсимбекова Г., Аубакиров А., Бейсенова А.* Балалар мен жасөспірімдердегі сүйек алмасуындағы биохимиялық маркерлардың рөлі. Әдебиеттік шолу // Ғылым және Денсаулық сақтау. 2025. Vol.27 (1), Б. 250-256. *doi 10.34689/SH.2025.27.1.027*

Introduction

Skeletal health is critical during childhood and adolescence, as it directly affects growth, development, and overall quality of life. Optimal bone development and maintenance require a precise balance between bone formation and resorption [22]. Two processes—remodeling and modeling—underlie the development and maintenance of the skeletal system. Bone modeling is responsible for growth and mechanically induced adaptation of the bone. [32]. Bone remodeling, a continuous process of old bone resorption followed by new bone formation, plays a fundamental role in preserving skeletal integrity, strength, and mineralization [15]. The primary molecular mechanisms underlying reduced bone mineral density are believed to involve increased osteoclast activity, decreased osteoblast activity, or both—resulting in an imbalance in the bone remodeling process characterized by accelerated bone resorption and impaired bone formation [20].

Peak bone mass attained during adolescence and the rate of bone loss in adulthood are key determinants of future osteoporosis risk [2,30]. In addition, the level of peak bone mass reached in adolescence directly influences the likelihood of pathological fractures and osteoporosis later in life [9, 13]. Disruptions in bone metabolism can lead to growth delays and various skeletal disorders, including osteoporosis and fractures [15, 27]. In pediatric populations, bone mineral content is commonly used to assess bone deficiencies and fracture risk [8, 35]. Bone health is evaluated through various methods, with dual-energy X-ray absorptiometry (DXA) recognized as the gold standard for bone density assessment [19, 21] In recent years, biochemical markers have become valuable tools for assessing bone metabolism and turnover [10]. Serum markers of bone formation include bone-specific alkaline phosphatase, osteocalcin, and the C- and N-terminal propeptides of type I collagen. Urinary markers of bone resorption include degradation products of type I collagen, such as pyridinoline (PYD), deoxypyridinoline (D-PYD), and the C- and N-terminal telopeptides of type I collagen (CTX and NTX) [16]. The assessment of biochemical markers of bone metabolism enables evaluation of bone status, determination of the rate of bone turnover and the extent of spontaneous bone loss, monitoring of osteoporosis treatment with antiresorptive agents, and prediction of fracture risk [17]. Several studies have demonstrated that bone turnover markers (BTMs) may provide information on fracture risk independently of bone mineral density (BMD); thus, incorporating them into risk assessment algorithms may enhance the prediction of fractures [33].

Bone metabolism markers are a group of biological molecules produced during bone tissue renewal and its regulatory processes, including bone matrix proteins, enzymes, and hormones. Compared to radiological methods, marker-based assessments may provide a more accurate reflection of bone metabolism [5, 29]. Osteoid production by osteoblasts is reflected in the formation of non-collagenous markers—such as bone-specific alkaline phosphatase (BALP) and osteocalcin (OC)—as well as collagenous markers, including the N-terminal propeptide of type I procollagen (PINP). Type I collagen is the most abundant collagen in connective tissue, with its highest synthesis occurring in bones, where it constitutes the majority of the organic bone matrix. Its precursor, type I procollagen, is synthesized by osteoblasts, and its terminal propeptides are cleaved extracellularly. Bone resorption, which involves the degradation of the organic bone matrix following enzymatic digestion, is assessed using resorption markers, such as degradation fragments of type I collagen—N- and C-terminal telopeptides of type I collagen (NTX and CTX)—as well as the release of tartrate-resistant acid phosphatase type 5b (TRAcP5b) [16, 24]. Laboratory analysis of bone turnover markers is non-invasive, sensitive, and rapid, making it useful not only for evaluating overall bone metabolism but also for monitoring the treatment of osteopenic conditions [34]. By measuring bone metabolism markers, clinicians can assess the overall metabolic state of bones and track dynamic changes in systemic bone tissue [12].

In children, bone turnover markers can be valuable for diagnosing and managing skeletal disorders; however, challenges in interpreting results may arise. The results obtained using different methods are not identical, with the discrepancies being particularly pronounced for β-CTX assays at higher concentrations typically observed in children, which necessitates method-specific reference intervals [7]. Compared to adults, children exhibit elevated levels of bone markers due to the rapid skeletal growth rate and high bone turnover. The selection of markers for assessing bone metabolism is based on several criteria, including bone specificity, clinical efficacy, biological and analytical variability, broad availability, potential for methodological standardization, sample processing requirements, stability, and measurement environment [24]. However, the interpretation of results is complicated by the

influence of multiple factors, such as age, pubertal stage, growth velocity, mineral accumulation, hormonal regulation, nutritional status, circadian and daily variations, bone tissue specificity, and the sensitivity and specificity of assays [31].

The use of discrete age strata allows for easy implementation into standard laboratory information systems. However, continuous reference intervals may be preferable, particularly when test results exhibit rapid changes with age [25]. The International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry (IFCC) recommend serum P1NP and CTX-1 as the preferred markers for bone formation and resorption, respectively, for fracture risk assessment and osteoporosis treatment monitoring [36].

Thus, for each pediatric population residing in a specific climate and sharing a similar lifestyle, reference values should be established based on age and sex. These reference values must be derived after validating the relationships between bone formation and turnover markers, accounting for age- and sex-related differences in subjects with similar lifestyles within the same geographic regions [40]. The onset and progression of osteoporosis is closely associated with factors regulating bone remodeling, such as calcium, vitamin D, estrogen, and parathyroid hormone (PTH). Vitamin D plays a crucial role in the bone remodeling process as it is involved in calcium homeostasis, which is essential for maintaining bone health. It enhances the absorption of dietary calcium in the intestines, reduces calcium loss in urine, and mobilizes calcium stored in the skeleton [18]. Vitamin D levels are an important factor in determining bone health. A deficiency of active vitamin D metabolites severely impacts the calcification of osteoid, leading to rickets in children and adolescents or osteomalacia in adults. It has been proven that skeletal manifestations of vitamin D deficiency are linked to a secondary contributing factor: hyperparathyroidism. This results in increased bone remodeling turnover, changes in calcium and phosphate metabolism, and consequently, an increased risk of osteopenia and osteoporosis [1]. In vitamin D deficiency, parathyroid hormone (PTH) is activated, playing a central role in the regulation of calcium-phosphate metabolism and its elevation in response to low serum calcium levels. Chronic hypersecretion of PTH most often leads to bone resorption [11].

In Kazakhstan, the assessment of bone metabolism markers in pediatric populations remains limited in clinical practice. We identified only two domestic publications that investigated infants under one year of age, with no published studies on children older than one year or adolescents [38, 39]. Therefore, the present literature review is highly relevant to address this gap.

This review aims to analyze the literature on the role of bone turnover markers and their reference values in children.

Search Strategy:

A systematic search was conducted in the electronic databases PubMed and Google Scholar using the following keywords: "bone metabolism markers," "osteopenic syndrome in children," "osteoporosis diagnosis," "C-terminal telopeptide," and "reference values of bone metabolism markers." The search was limited to studies published in English over the past 10 years.

Inclusion Criteria: studies were included in the review if they met the following criteria: (1) data on the use of bone metabolism markers in somatically healthy children and adolescents; (2) information on the role of bone metabolism markers in pediatric populations; (3) studies published in English; (4) diagnostic studies assessing the early detection of reduced bone mineral density; (5) research evaluating the diagnostic role of bone metabolism markers.

Exclusion Criteria: the following studies were excluded: (1) research focusing on adult populations with bone disorders; (2) articles without full-text availability; (3) studies with low methodological quality, such as case reports and case series; (4) publications in languages other than English, (5) studies that did not assess bone metabolism markers.

A total of 40 sources were reviewed, describing the role of bone turnover markers in healthy children and adolescentsand their association with various pathologies. However, only five studies met our inclusion criteria.

Ethical Statement: This literature review was based on previously published studies; therefore, ethical committee approval and patient consent were not required.

Discussion

In the analysis of the selected studies, we examined the levels of osteocalcin, C-terminal telopeptide of type I collagen (CTX-I), N-terminal propeptide of type I procollagen (PINP), and alkaline phosphatase in the blood of healthy children and adolescents from Poland, Korea, China, Portugal, and Italy.

A study conducted by Gajewska J et al. (2024) examined 355 healthy children and adolescents from Poland with normal weight (46.5% girls) aged 1 to 18 years. Bone mineral density (BMD) was assessed using dual-energy X-ray absorptiometry (DXA), and bone turnover marker concentrations were measured using immunoassay methods.

The study findings revealed significant variations in bone marker levels among adolescents, with notable gender differences:

- Median alkaline phosphatase (BALP) levels at ages 14–15.9 and 16–18 years were significantly higher in boys than in girls ($p < 0.001$; $p = 0.022$, respectively).
- Median osteocalcin (OC) levels at ages 12–13.9, 14–15.9, and 16–18 years were higher in boys than in girls ($p = 0.019$; $p = 0.010$; $p = 0.018$, respectively).
- Median C-terminal telopeptide of type I collagen (CTX-I) levels at ages 14–15.9 years were higher in boys than in girls ($p = 0.004$).

Statistically significant positive correlations were observed across the entire study population, as well as in gender-specific subgroups:

- CTX-I and osteocalcin levels ($r = 0.664$, $p < 0.001$; $r = 0.687$, $p < 0.001$; $r = 0.645$, $p < 0.001$, respectively).
- CTX-I and alkaline phosphatase levels ($r = 0.207$, $p < 0.001$; $r = 0.256$, $p = 0.001$; $r = 0.173$, $p = 0.017$, respectively).
- Osteocalcin and alkaline phosphatase levels, both in the total study group and in the female subgroup ($r = 0.170$, $p = 0.001$; $r = 0.219$, $p = 0.005$, respectively) [14].

In 2019, Choi JS et al. conducted a study to assess the association between N-terminal propeptide of type I procollagen (P1NP) and osteocalcin with age and sex in a cohort of healthy Korean children and adolescents.

The study included 580 participants (290 boys and 290 girls), aged 0–18 years, recruited from outpatient clinics in Korea. Significant age-related changes in bone turnover markers were observed in both sexes ($p < 0.001$), along with notable differences between boys and girls ($p < 0.05$).

• P1NP levels were highest during the first year of life, after which they gradually declined, with some fluctuations leading up to puberty.

• In boys, P1NP levels tended to rise during puberty, whereas in girls, they showed a steady decline with age.

• Unlike P1NP, osteocalcin did not exhibit a distinct postnatal peak. Instead, its levels increased with age in both sexes, peaking at 11–13 years in boys and 9–12 years in girls.

• A significant positive correlation was found between serum P1NP and osteocalcin levels ($r = 0.467$, $p < 0.001$) [6].

Table 1.

Reference values of bone metabolism markers in children and adolescents.

№	Author, year of publication	Country	Total sample, age	OC[1] ng/mL	CTX-1[2] ng/mL	P1NP[3] µg/L	(BALP)[4] U/L	*P**
1	Gajewska J., 2024 [1]	Poland	355(0-18)	83.2 (52.6-114.4)	1.70 (1.19-2.12)	-	112.1 (87.9-132.5)	< 0.004
2	Choi J.S., 2019 [22]	South Korea	290 (0-18)	67.3–108.8	-	519.6–1966,9	-	< 0.001
3	Zhang Y., 2023 [33]	China	661(0-16)	-	-	61–1399	-	< 0.001
4	Monjardino T., 2019 [44]	Portugal	395 (7)	51.3 – 133.8	0.470-1.690	-	159 - 439	< 0.002
5	Brescia, 2024 [5]	Italy	202(1-14лет)	25.33-190.07	0.48-2.86	-	22.32-163.54	< 0.05
6	Larsen J.B., 2021 [6]	Northern Europs	420(2-18 years)	-	-	18-62 15-75	-	< 0.001

[1] OC- Osteocalcin, [3] P1NP -N-terminal propeptide of type I procollagen,
[2] CTX-1- C-terminal telopeptide of type I collagen, [4] BALP - Alkaline phosphatase.

According to a 2023 study by *Zhang Y. et al.,* a total of 366 boys and 295 girls aged 0–16 years from Southwest China participated in the research. The participants were categorized into three age groups: preschool (boys and girls aged 0–6 years), prepubertal (boys aged 6–12 years and girls aged 6–10 years), and adolescent (boys aged 12–16 years and girls aged 10–16 years). The study found that P1NP levels in boys decreased with age until the prepubertal stage, after which they began to rise. Significant differences in P1NP levels were observed between the preschool and adolescent groups ($p < 0.001$ and $p = 0.007$, respectively). Meanwhile, levels of C-terminal telopeptide of type I collagen (CTX-I) and N-terminal mid-fragment of osteocalcin increased with age in boys. Statistically significant differences in these markers were noted between the preschool and prepubertal stages ($p < 0.001$ and $p = 0.006$, respectively), between the preschool and adolescent stages ($p < 0.001$ for both markers), and between the prepubertal and adolescent stages ($p < 0.001$ for both markers) [37].

In a 2019 study, *Monjardino T. et al.* highlighted that single-time-point measurements of bone metabolism markers have limited utility in describing anthropometric growth and overall bone health in generally healthy prepubertal children. The study evaluated 395 seven-year-old children from a Portuguese cohort. When comparing BMI groups, the researchers observed that overweight children had significantly higher alkaline phosphatase concentrations than those with normal weight ($p = 0.002$). However, no differences in serum osteocalcin and C-terminal telopeptide (CTX) concentrations were detected across BMI groups or weight gain trajectories. Furthermore, CTX showed no correlation with any bone parameters measured via DXA [28].

Brescia et al. in a 2024 study assessed reference intervals for bone metabolism markers in Italian children and adolescents. The study included a total of 202 participants aged 1 to 18 years. Significant differences ($p < 0.05$) were found in median alkaline phosphatase concentrations, with higher levels in the 13–18 age group compared to the 1–6 and 7–12 age groups. Additionally, notable sex-based differences ($p < 0.05$) were observed in alkaline phosphatase levels, particularly within the 13–18 age group. The study also reported significant variations ($p < 0.05$) in median CTX concentrations, with higher levels in the 13–18 age group compared to younger age groups. Furthermore, CTX concentrations differed significantly ($p < 0.05$) between males and females, with particularly strong statistical significance in the 13–18 age group ($p < 0.0001$) [4].

Bayer, M. (2014) investigated the relationships between bone formation markers, bone turnover markers, and variables such as age, gender, and pubertal stage in a cohort (n = 439) of healthy children and adolescents of European descent. The highest levels of PINP were observed during the first year of life. No postnatal peak for OC was found; however, its levels remained higher than the reference interval for adults throughout childhood. OC reached its peak during the pubertal growth spurt, at the second to third stages of Tanner breast development in girls and at the second to third stages of Tanner genital development in boys. PINP peaked during the second to third stages of Tanner breast development in girls and at the third stage of Tanner genital development in boys [3].

Larsen J.B. et al. (2021) in their study determined the serum level of PIIINP, which were analyzed in healthy blood donors aged 19–67 years (n = 240) and children aged 2–18 years (n = 420). PIIINP levels were influenced by age but not gender. The following reference intervals were established: 2–10 years, 18–62 µg/L; 11–18 years, 15–75 µg/L; 19–39 years, 15–55 µg/L; 40–67 years, 14–31 µg/L. In conclusion, age-specific reference intervals for PIIINP using the MAGLUMI 800 CLIA were indicated in a large Danish cohort. These results may be useful for other laboratories wishing to set up PIIINP on the same platform and may provide improved recommendations for clinicians [23].

The role of vitamin D in bone metabolism is well-established in both children and adults. In their study, *Marwaha et al.* (2019) investigated the status of bone markers in children with vitamin D deficiency across four schools in India. The study included 468 children and adolescents. These participants, with preserved samples taken before and after supplement intake, along with available anthropometric data,

serum biochemistry, 25-hydroxyvitamin D, and parathyroid hormone levels, were evaluated for markers of bone formation (aminoterminal propeptide of type 1 procollagen [P1NP]) and resorption (β-crosslaps [CTx]). Following supplementation, a significant reduction in serum P1NP levels (from 691 ± 233 ng/mL to 640 ± 259 ng/mL, P < 0.001) and CTx levels (from 1.67 ± 0.53 ng/mL to 1.39 ± 0.51 ng/mL, P < 0.001) was observed. While reductions in both P1NP and CTx levels were noted in both boys and girls, the effect was more pronounced for serum CTx levels compared to P1NP levels across all three supplement intake groups and vitamin D deficiency (VDD) categories [26].

Conclusion. This review highlights the importance of assessing bone metabolism markers in children and adolescents. Establishing age-specific reference intervals for these markers, considering ethnic and geographic variations, can be clinically valuable in evaluating bone metabolism. The determination of reference ranges for osteocalcin, C- and N-terminal procollagen type I propeptides, and alkaline phosphatase as biochemical markers of bone formation is essential for their clinical application in pediatric practice.

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