

## BONE CHANGES, MINERAL HOMEOSTASIS IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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**Summary.** *In childhood acute lymphoblastic leukemia [ALL] skeletal changes are frequently found at the time of diagnosis and treatment, including: metaphyseal lines, periosteal reaction, lysis, sclerosis, osteoporosis and occasionally spontaneous fracture.*

*Different factors, including the disease itself, may be responsible for a defective bone homeostasis in these patients. Soluble products of malignant cells like the osteoclast activated factor (OAF), lymphotoxin, IL-1, tumor necrosis factor (TNF) and other cytokines may cause bone demineralization. Cytotoxic drugs, like methotrexate corticosteroids and radiotherapy, have been incriminated as elements of the treatment that may cause bone changes.*

*Prospective analysis of the bone and mineral status in 108 children with ALL was performed. Markers of bone turnover (Ca, P, Mg homeostasis in urine and serum, osteocalcin and PTH) were measured before the initiation of the therapy, on the 28<sup>th</sup> day of therapy and six months after it. The bone mass was determined on the x-ray and densitometry was measured.*

*At the time of diagnosis musculoskeletal pain was present in 37.5% of patients. It was common in children with better prognosis (CD 10 immunophenotype, low leucocytes count, L1-morphology).*

*We found hypocalcemia, hypomagnesaemia and calciuria. PTH and osteocalcin decreased at the time of diagnosis 80% children with ALL had decrease bone mineral density.*

**Key words:** *Acute lymphoblastic leukemia, childhood, bone changes*

### Introduction

Leukemia is the most common cancer in children and may affect virtually all organ systems. Skeletal abnormalities have been described in association with ALL, including juxtametaphyseal lucent bands or "leukemic lines" in long bones, osteoporosis, periosteal reaction, reactive sclerosis, lytic defects, vertebral compression fractures (1-5).

Children with ALL often have bone pain and disturbances of gait. Reduced bone turnover has been reported at diagnosis and during the treatment of ALL (3). The cause is most probably multifactorial.

The disease itself plays a role. Soluble products of malignant cells like lymphotoxin, IL-1, IL-8, TNF, OAF may be the cause of bone demineralization (4). Treatment with corticosteroid decreased bone formation and increased bone resorption with consequent net loss of bone mineral (6). Methotrexate, doxorubicin, and radiotherapy play a role in these changes (7,8).

### Materials and methods

**Patients:** We have studied 108 children (67 boys, 41 girls) medium age 6.19 years; range 2-16 years, with ALL. All children were diagnosed at the Children Hospital in Niš and Belgrade. Protocol treatment was AIEOP-95.

Patients were divided into two groups as follows:

Group I: No bone pain patients

Group II: Bone pain patients

Investigation was at diagnosis, on the 28<sup>th</sup> day of the therapy and six months after the therapy.

**Biochemical methods:** Blood and urine levels of calcium and magnesium were measured by standard spectrophotometry ionized Ca by ion-selective electrodes, phosphorus, alkaline phosphatase by standard biochemical methods.

PTH and osteocalcin by radioimmunoassay. We measured bone mineral content with single-photon absorptiometer.

BMD were measured of lumbar vertebrae (L2-L4).

**Statistic:** Data are expressed as mean value  $\pm$  standard deviation (SD), range.

## Results

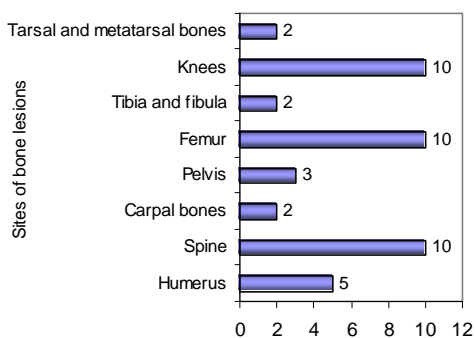
**Clinical assessment:** Of the 108 children 40 (37.05%) had musculoskeletal pain. 18 (16.67%) had pain at diagnosis, 10 (9.26%) had pain after the induction therapy and 12 (11.12%) 6 months after the therapy.

Pain in the lower extremities and spinal locations is more frequent. 8/40 had back pain, 10/40 had pain in knee joint, 8 had in femur and tibia.

Changes of spongiosa were more frequent than changes in cortex. Trabecular bone is more sensitive to metabolic changes than cortical bone.

Children in group 2 had skeletal changes and bone pain. They were older than children in group 1. Medium age in group 2 was  $7.6 \pm 3.4$ , but in group 1. it was  $5.37 \pm 2.7$ , ( $p < 0.001$ , t-test). Children with bone pain were older.

Children younger than 2 years didn't have bone pain and bone changes.



Graph. 1. Sites of bone lesions found in 40 children presented with acute lymphoblast leukemia

Some children had changes in two sites of bone. Children with musculoskeletal symptoms (group II) had a longer duration from onset of illness to diagnosis (mean 5.5 weeks) compared with those without pain (mean 3.0 weeks).

In group I patients had leukocyte counts in less than  $20 \times 10^9$  cells/L ( $20000/\text{mm}^3$ ) and most had the expression of CD 10 (CALLA) immunophenotype (78%).

Table 1. Leukocyte counts and blast counts in I group and II group

At diagnosis	I group	II group	t-test p
Leukocyte $\times 10^9$	$79.488 \pm 22.4$	$13.01 \pm 20.8$	$p < 0.001$
Blasts No	44 271	13 666	$p < 0.001$

Table 2. Radiologic examination: Skeletal abnormalities

Skeletal abnormality	No	%
Osteopenia	30	27.78
Dense bands	16	14.82
Lytic lesions	7	6.48
Periosteal reaction	2	1.85
Partially vertebral compression	4	3.70
Fracture	1	0.93



Fig. 1. Rø knees in child with ALL. Knees with diffuse and severe demineralization, lytic defects and horizontal radiolucent bands.



Fig. 2. Rø spine in children with ALL. Demineralisation and partially vertebral compression.

### Bone mineral mass (BMD)

Bone mineral density was decreased in 86% of patients at diagnosis and during the therapy. Z-score was  $-0.22$  to  $-1.96$ . One patient had femoral fracture and BMD 66% of normal range.

Two children had normal BMD for their age.

### Biochemistry

Biochemical measurements of mineral status are summarized in Table 4. Examination was at diagnosis (I

Table 3. Biochemical measures of mineral and endocrine status

Serum measurements	I group	II group	III group	normal range
Total Ca mmol/l	2.17 ± 0.17	2.18 ± 0.21	2.30 ± 0.11	2.25 – 2.75
Ionic Ca	0.98 ± 0.06	1.08 ± 0.07	1.1 ± 0.08	0.9 – 1.18
Mg	0.85 ± 0.11	0.83 ± 0.1	0.90 ± 0.14	0.77 – 1.02
P	1.51 ± 0.41	1.35 ± 0.45	1.57 ± 0.30	0.9 – 1.9
Alkaline phosphatase (U/L)	176.43 ± 86.0	212.23 ± 84.8	345 ± 120	90 – 446
PTH (pg/ml)	21.94 ± 16.8	30.86 ± 17.8	26.85 ± 11.13	12 – 70
Osteocalcin (ng/ml)	15.63 ± 9.1	49.56 ± 23.6	41.22 ± 14.3	10 – 40

group) on the 28<sup>th</sup> day of the therapy (II group) and 6 months after the therapy (III group).

In group I 12.37% patients had marginal hypocalcemia and 9.26% had mild ionic hypocalcemia.

In group II 13.89% had hypocalcemia, one patient had hypercalcemia (2.85 mmol/l) –0.9%

Children in postchemotherapy group were normocalcemic.

Hypomagnesiemia was detected in 23.53% of children.

Plasma magnesium values rose significantly after the completion of chemotherapy.

Phosphorus concentration fell within the normal range. Alkaline phosphatase activity also rose significantly in the off – therapy period.

Parathyroid hormone levels were low in 11.10% of children. 15.62% patients had initial plasma osteocalcin levels that fell below the normal reference range.

Values of osteocalcin and PTH rose significantly after the completion of chemotherapy.

Hypercalciuria was detected in 58.33% of children.

## Discussion

The bone and joint lesions caused by acute leukemia are significantly more frequent and sever in children than in adults (37.05%) (9).

The bone pain is related to loss of bone mineral mass and perturbation of mineral homeostasis.

These abnormalities increase in frequency and severity as treatment progresses, and begin to resolve after therapy has been completed, suggesting that treatment of ALL plays a role in the pathogenesis of osteopenia (10,11).

Alternatively there may be an indirect effect from a soluble products of the malignant cells.

In addition the effects of chemotherapy on gastrointestinal and renal handling of nutrients may cause alterations in mineral homeostasis that eventually lead to abnormal turnover of bone mineral. Malnutrition, resulting from inadequate dietary intake, did not appear to be a major contributing factor in the abnormal BMC in

our patients. The reduced bone mass may be the results of defective mineralization (12). Decreased intestinal absorption of magnesium would be a likely explanation for this finding, because urinary magnesium excretion was normal or low.

Hypocalcemia is prominent manifestation because of reduced PTH secretion.

Hypercalciuria was a common finding in our patients during therapy. All of our patients had PTH levels below the upper limit of the normal range, perhaps indicating an inappropriately low PTH response in those with mild hypocalcemia.

Abnormal bone turnover in our patients was indicated by the measurements of plasma osteocalcin, (which is synthesized by osteoblasts and it is index of bone turnover).

The mean osteocalcin value in these children fell below the normal range and rose significantly in all children after the treatment.

The low BMC during therapy in the majority of our patients is compatible with biochemical findings.

Other investigators have reported similar observations (13).

We can explain the skeletal involvement in children with ALL and the hematological disease with the intimate relation between the bone marrow and bone cells development (14). Cells of the bone and the hematopoietic bone marrow share progenitors, produce and respond to some of the same cytokines and colony-stimulating factors. Both osteoclasts and osteoblasts originate in the marrow.

## Conclusion

Leukemia in children may mimic several orthopedic condition when the patients is seen first. Radiographic manifestations are suggestive but not pathognomonic of leukemia. Bone pain can be the first symptom of leukemia (15). As the initial presentation of leukemia commonly involves the musculoskeletal system, the pediatrician must have a high index of suspicion.

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## **KOSTNE PROMENE, MINERALNA HOMEOSTAZA U DECE SA AKUTNOM LIMFOBLASTNOM LEUKEMIJOM**

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*Kratak sadržaj: Dece koja boluju od akutne limfoblastne leukemije imaju skeletne promene na početku bolesti i u toku tretmana. Uočavaju se metafizealne linije, periostalna reakcija, osteoliza, osteoporoza i spontane frakture. Različiti faktori, uključujući i samu bolest, mogu biti odgovorni za izmenjenu kostnu homeostazu kod tih pacijenata. Solubilni produkti malignih ćelija kao što su osteoklast aktivirajući faktor (OAF), limfotoksin, IL-1, TNF i drugi citokini mogu biti uzrok kostne demineralizacije. Citotoksični lekovi kao što je methotrexat, zatim kortikoterapija i radioterapija, smatraju se elementima koji dovode do promena kostnog metabolizma. Urađena je prospektivna analiza kostnog i mineralnog statusa 108 dece sa akutnom limfoblastnom leukemijom. Marker kostnog "turnover"-a (Ca, P, Mg u urinu i serumu, osteokalcin i parathormon) mere se na početku bolesti, 28. dana posle indukcije i nakon završene terapije. Muskuloskeletni bol uočava se kod 37,5% pacijenata. Ovaj simptom je u korelaciji sa parametrima bolje prognoze (CD 10 imunofenotip, manji broj leukocita na početku bolesti, L1 morfoloģija). Uočava se hipokalcemija, hipomagnezijemija, kalciurija i smanjenje PTH i osteokalcina u trenutku dijagnoze. 80% dece ima smanjenje kostne gustine.*

**Ključne reči:** *Akutna limfoblastna leukemija dece, kostne promene*