*REVIEW ARTICLE*

# Alteration in Bone Mineral Metabolism in Children with Acute Lymphoblastic Leukemia (ALL) : A Review

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**Abstract**

In recent years there has been a significant increase in event free survival (EFS) and overall survival in children with cancer. As survival rates for childhood cancer have radically improved, late effects associated with the successful but highly intensive chemotherapy and/or radiotherapy have dramatically increased. Many possible late effects of cancer treatment are recognized in pediatric cancer patients as infertility, endocrine deficiency, renal failure, pulmonary and cardiac toxicity, obesity and osteopenia/osteoporosis. Decreased bone mineral density (BMD) and bone metabolism disturbances have been recognized and reported in literature. Osteopenia/osteoporosis skeletal abnormalities, osteonecrosis and pathological fractures are known to occur frequently in childhood acute lymphoblastic leukemia (ALL) at diagnosis, during and after treatment with chemotherapy. Various studies have revealed different metabolic alterations related to ALL. Some suggestions have been made about their relationship with the disease process. Various metabolic abnormalities may be encountered in the newly diagnosed ALL patients. It includes decreased and increased serum levels of calcium and phosphate. Hypercalcemia may result from leukemic infiltrations of bone and release of parathormone like substance from lymphoblast. Elevated serum phosphate can occur as a result of leukemic cell lysis and may induce hypocalcemia. It has been postulated by other authors that leukemic cells may directly infiltrate bone and produce parathroid hormone related peptides, prostaglandin E and osteoblast inhibiting factors. Hypomagnesemia, hypocalcaemia and hypothyroidisum have been demonstrated in patients with ALL. Some patients may have poor nutrition and decreased physical activities during treatment. However postulations have also been made that chemotherapy may play a role in creating metabolic alterations in children with ALL. Corticosteroid, methotraxate and cranial irradiations have all been assumed as a cause of loss of bone mass. Continuing chemotherapy in children with ALL was assumed with normal growth and normal or high collagen turnover and reduced alkaline phosphatase or impaired osteoblastic activity on mineralization of bone. Considering the derangements in bone mineral metabolism in ALL at diagnosis or with chemotherapy, it is imperative that specific attention and therapeutic measures should be considered.

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## Introduction

Developments in diagnostic and therapeutic procedures have led to increased survival rates in childhood cancer[1]. Approximately two thirds of the patients are cured and reach adulthood. Many of the adverse effects of cancer treatment such as growth retardation, cardiomyopathy and effects on fertility are well recognized. Skeletal problems including osteopenia, osteoporosis and pathological factures have also been recognized in children with cancer[2-4].

Acute lymphoplastic leukemia is the most common pediatric malignancy. The overall 5 years survival rate exceeds 70%, yielding an increased population of survivals. Processes potentially disruptive to bone metabolism during childhood and adolescence may place survivors of childhood ALL at increased risk for reduced peak bone mass and fractures earlier in life[5]. Musculoskeletal disorders are well known complications of ALL and its treatment. Children with ALL often have bone pain, disturbances of gait and fractures. Reduced bone turnover and bone mineral density (BMD) have been reported at diagnosis and during treatment of ALL. Also in long-term survivors of ALL reduced BMD has been found. The cause is most probably multifacorial . The disease itself as well as its treatment such as corticosteroids, methotrexate and radiotherapy may play a role[6].

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**Mineral and bone metabolism:** Calcium is the fifth most common element and the most prevalent cation found in

the body[7]. An average human body contains approximately one kg of calcium. Calcium has many important physiological functions in the cells, including muscle contraction, hormone secretion, glycogen metabolism and cell division[7]. Calcium is found in three main compartments-the skeleton, soft tissue and extra vascular fluid[7,8]. The skeleton contains 99% of the body calcium predominantly as extra cellular crystal of unknown structure with a composition apparently that of hydroxyapatite. In blood virtually all of the calcium is in serum or plasma which has mean normal concentration of approximately 9.5 mg/dl (2.37 mmol/L). Calcium exists in three physiochemical state in plasma of which 50% is free or ionized. Another 40% is bound to plasma protein chiefly albumin.

The major roles of the skeleton are to provide structural support for locomotion and to protect vital internal organs. The skeleton is also a major store house for providing calcium for the extra cellular and intra cellular pool. Approximately 5 gm of calcium is rapidly available for the skeletal exchange-pool and is accountable for maintaining normal physiological function[8] .

**Phosphate:** Phosphorus in the form of inorganic phosphate is an important and widely distributed element in human body[7]. An adult human has approximately 600 gm of phosphate expressed as phosphorus of which 85% is in skeleton and rest in the soft tissue. Although bone in organic phosphate are present mostly in organic form, phosphate also incorporates into nucleic acid, phospholipids, phosphoprotein and high energy compound involving cellular integrity and metabolism. Plasma contain approximately 2.5-4.5 mg/dl as organic phosphate which is generally the major part in biochemical tests.

**Physiological function:** Phosphate has several diverse actions in cells. It has a critical role in high energy phosphate found in adenosine triphosphate and other high energy compounds. The energy sources maintain many physiological functions such as muscle contractility, neurological function and electrolyte transport. Phosphate is a constituent of cyclic adenine and guanine as well as nicotinamide adenodimidine phosphate which are important in many enzyme system[9].

Extracellular phosphate maintain the critical intracellular concentration and provide substrate in bone mineralization. Acute decline in the serum phosphate concentration may result in rapid complications such as rhabdomyolysis and altered red cells functions[7].

**Mineral homoestosis and bone mass in children treated for ALL:** Acute lymphoblastic leukemia is the most common malignancy in childhood[10]. Now a days with current treatment survival and life expectancy has increased in ALL. The treatment of children with ALL with intensive chemotherapy is associated with long-term disease free-survival, but there are many deleterious side effect of therapy. Some of the long-term problems of ALL patients include biochemical disturbances of vitamin D and minerals, reduction of mineral content of bone and pathological fractures due to osteoporosis[11].

Skeletel abnormalities have been described in association with ALL including vertebral compression fractures, osteoporosis and juxtrametaphyseal lucent bands or "leukaemic" lines in long-bones[3]. It has been shown that mild ionic hypocalcemia and hypomagnesemia were present in nine and eight of 16 children respectively. Hypercalciuria were also present. Alkaline phosphates activity was increased significantly after therapy.

Asadi et al had studied 20 patients aged 8$\pm$2.4 years. Average serum calcium levels was 9 mg/dl before chemotherapy and 9.4 mg/dl after chemotherapy[11]. Differences of phosphorous and alkaline phosphatase was not significant. Sixty five percent of patients had hypercalciuria before chemotherapy but it has decreased subsequently. It seems that disturbances of mineral and specially calcium metabolism are common in ALL patients. Chemotherapy have not been found to have considerable effect on calcium mineral levels rather it appears that induction chemotherapy control the disease process with reduction of hypercalcemia.

Hypercalcemia and malignancy has been correlated with three causes in pediatric malignancy[12].

(1) Osteolytic bone lesion (particularly in T-cell leukemia and lymphoma)

(2) Bone demineralization secondary to parathyroid like factor.

(3) Immobilization.

Vander Sluis et al studied 61 cases of ALL and found mean calcium level at baseline which increased significantly during treatment. Phosphate was normal at diagnosis and decreased significantly in 32 weeks of treatment[6].

Other putative causes of impaired bone mineralization are both leukemic infiltration and expansion of the bone marrow that might destroy the spongiosa and various factors secreted by leukemic cells such as ectopic production of PTH and PTH related peptide[13]. Guo et al

reported that the changes of biochemical markers of bone turnover is consistent with the result of a study in which children with a solid tumour or ALL were treated with chemotherapy for one year[14]. In that study bone formation markers increased significantly with the start of chemotherapy where bone repair markers did not change after completion of chemotherapy.

Athassinodu et al in their study found biochemical markers only for alkaline phosphatase to be significantly different between controls and ALL patients[15]. Croften et al reported decreased values of bone forming markers at diagnosis of ALL which could be related to disease itself and there has been increase in the values after intensive chemotherapy[16].

Hypomagnesemia is a recognized complication in the treatment of ALL. The mechanism by which hypomagnesemia occurs and nature of the association between hypomagnesemia and bone mineral accretion in children with ALL during chemotherapy are unclear[14]. Altered nutritional status and renal magnesium wasting results from the administration of amynoglycoside antibiotic. Aminoglycoside such as gentamicin may contribute to the magnesium deficiency in such children. Magnesium wasting has been reported to be associated with such antibiotic therapy in adults and even in children treated with higher dose of these drugs who did not have ALL[2].

Skeletal magnesium represents 54 percent of total body magnesium content. During bone formation extracellular magnesium enters into the skeletal magnesium pool to support bone mineral acquisition. It is possible that the hypomagnesimia observed in the first six month of chemotherapy in children with ALL is a function primarily of the rapid recovery of bone mineralization[14]. Binky et al comments that mild hypomagnesimia has been observed in children with leukemia who received amikacin empirically for fever in the context of neutropenia[9]. There has been no evidence of tubular injury. Rather functional site of renal injury leading to aminoglycoside mediated magnesium wasting is the thick ascending loop of Henle[17].

Arikosi et al in their one year prospective study has shown that absolute height (cm), relative height (SDS cm) and BMI did not differ significantly between the patients and their age and sex matched control at diagnosis and after one year of treatment in newly diagnosed children with cancer. However growth velocity during the one year follow up was significantly lower in patients than in controls[1]. Serum values of calcium, magnesium, alkaline phosphatase were significantly decreased at diagnosis compared to normal values.

**Effects of glucocorticoids on bone resorption and mineral metabolism**: Glucocorticoids such as dexamethasone and prednisolone is a constituent of chemotherapeutic regimen in different stages of induction, intensification and maintenance of ALL. Glucocorticoids enhance bone resorption, decrease bone formation and consequently they decrease bone mass and increase the risk of fractures[18]. The increased bone resorption is in part due to direct effects of glucocorticoids on the skeleton and in part the result of a decrease in intestinal calcium absorption and an increase in urinary excretion of calcium.

In vivo glucocorticoids inhibit intestinal calcium transport, opposing the effect of vitamin D but the mechanism has not been established. Serum levels of vitamin D metabolites in patients receiving glucocorticoids are virtually normal, and glucocorticoids induce the expression of calbindin D28 K, a protein involved in intestinal calcium transport[19].

Para-thyroidectomy prevents the excessive bone resorption associated with glucocorticoids suggesting that in vivo cause of excessive bone resorption is enhanced secretion or action of PTH. Glucocorticoids enhance the responsiveness of osteoblasts to PTH by increasing the expression of PTH receptor in these cells. As the bone resorping actions of PTH require the presence of osteoblasts, an increase in PTH receptors in osteoblasts by glucocorticoids could explain some of the result[20].

In vitro glucocorticoids have an acute stimulatory effect on bone resorption but in long-term they are inhibitory. The stimulation may be due to an increase in osteoclast activity and is in accordance with effects observed in vivo. The mechanism of this increased activity is not known although it could involve the induction of interleukin-6(k-6) receptors in skeletal cells[21].

**Conclusion:**

So it seems that disturbances of mineral and specially calcium metabolism are common in ALL patients. Particularly bone metabolism in children with ALL after induction chemotherapy is disturbed resulting in a reduced BMD. The mechanism of this reduction could be multifactorial and having related to the disease itself, chemotherapy, radiotherapy and physical inactivity. However no factors were marked that would identify the individuals most at risk.

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