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Bone Density in Pediatric Patients with Acute Lymphoblastic Leukemia (ALL): A Literature Review

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Abstract

Introduction

Acute Lymphoblastic Leukemia (ALL) is the most common malignancy in children and the main form of childhood leukemia (75%). ALL different treatment options have a great impact on children weight and appetite. The improving prognosis for children with cancer refocuses attention to long-term outcomes with an emphasis on quality of life. More survival rate allows researchers to evaluate long term complication of ALL and its different treatment options such as endocrine abnormalities for example decreased bone mineral density.

Materials and Methods

A systematic web base search was conducted in MEDLINE up to December 2014. We included articles with available abstract in English language, and participants younger than 18 years. Manual searching was done within the reference list of articles. Two reviewers independently reviewed and assessed eligibility criteria, assessed quality, and extracted data.

Results

Trace elements concentration decline due to malabsorption or inadequate intake in children with ALL. Osteopenia occurs more frequent in younger children and those who treated with higher doses of corticosteroids.

Conclusion

The dietary history of ALL patients who are at more risk for fractures and osteopenia should be screened by paying more attention to calcium and vitamin D intake.

Key Words: Acute lymphoblastic leukemia, Children, Bone density, Vitamin D.

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Introduction

Despite recent scientific progress, etiology of childhood leukemia is still unknown. It is a multifactorial condition in which genetic and environment have important role (1). Chromosome translocation frequent occurrence is confirming for leukemia genetic base. Patients with Down syndrome, Ataxia telangiectasia and Wiskott aldrich syndrome would be at more risk for developing leukemia. Leukemia is more common in children who have siblings with malignancy (2). Its risk increases in twins. Some of environmental factor which are associated with leukemia are: Ionizing radiation, some bacterial and viral infections and chemotherapy and alkaline agents. Alcohol and smoking habits might relate to ALL. Its prevalence is slightly higher in white race. Male gender is a prognostic factor for ALL. ALL peak age is between 2 and 5 years (2, 3). Annually, 2500 to 3500 leukemia cases have been diagnosed in the United States of America (4). Its incidence is 40 in each one million children younger than 15 years. Acute lymphoblastic leukemia is the main form of childhood leukemia (75%).

Chronic forms of are very rare in childhood. Neoplastic diseases are the main second cause of childhood death in all around world. Lymphoid leukemia incidence has been increased 1% per year in recent two decades (5). ALL survival rate has been improved regard to new inventions in radiotherapy technology and chemotherapy agents. And also supporting care services and patients close follow up lead to increase survival rate from zero in 1950 to 80% in recent years (6). More survival rate allows researchers to evaluate long term complication of ALL and its different treatment options. One of the most important categories of these complications is endocrine abnormalities which include hypothyroidism, metabolic syndrome and insulin resistance growth retardation, decreased bone mineral density and Growth Hormone (GH) deficiency (7). ALL different treatment options have a great impact on children weight and appetite. A nutrition status has a great impact on ALL prognoses. Malnutrition influence growth indexes in children such as weight, height and arm circumference. It has been confirmed that children whose weight and height are 2 Standard Deviation (SD) lower than normal have poor prognoses. And malnutrition causes intolerance to chemotherapy (8). This study was designed to assess bone mass density in childhood ALL and the efficacy of calcium and vitamin D supplement.

Materials and Methods

Articles were selected by searching the Cochrane Library and MEDLINE up to December 2014. Our key word and Medical Subject Headings (MESH) were broad terms such as "Acute lymphoblastic leukemia" AND "Bone mass density" AND "Calcium" AND "Vitamin D".

Retrieved articles were assessed to identify additional related articles from their reference list. We included articles with available abstract, full text in English language. Manual searching was conducted within the reference list of articles. Firstly, abstracts were reviewed by two independent researchers. So, 32 abstracts were screened for relevancy two times. Seventeen of them were excluded due to no relevancy. The remaining 15 abstracts were fully assessed by our two reviewers. Regard to article type, 2 case reports and 2 reviews were excluded from further evaluation. We used consort quality appraisal from to assess the quality of selected studies.

Two reviewers independently scored the quality criteria for each included study and a third reviewer resolved any discrepancies. We used a structural data extraction tool. But due to heterogeneity in hormone and

outcome measurements, a Meta analysis was not performed. The flow diagram of literature search is shown in (Figure.1).

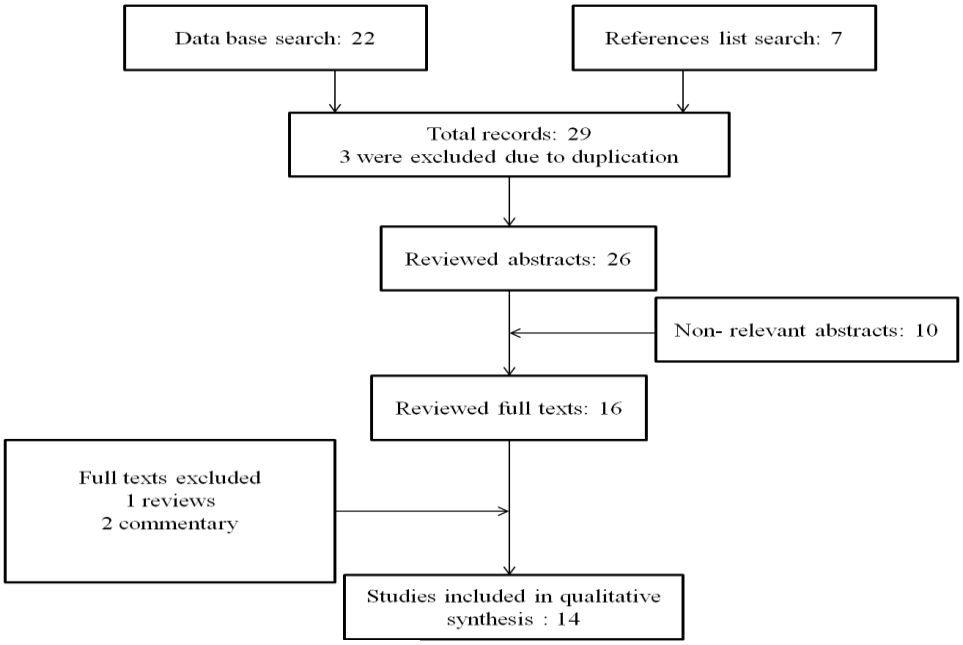

Fig.1: Diagram of literature search

Results

The oldest study was published in 1995 and the most recent one in 2014. Table.1 shows the general characteristics of the included studies.

1335 children with ALL were evaluated in these 14 studies. Three studies were randomized controlled trials, and other 11 ones were cohort studies.

Table1: Summary of the 15 studies included in the review

Reference NO.	Year	Target population	Sample size	Design	Final result
9	2014	Male children	215	cohort	ALL treatments did not increase bone turnover.
6	2014	children	275	RCT	ALL treatments lead to bone turnover.
10	2012	children	50	cohort	ALL treatments lead to bone turnover.
11	2012	children	18	cohort	ALL treatments lead to bone turnover.
12	2012	children	164	cohort	ALL treatments lead to bone turnover.
13	2010	children	70	cohort	85% of the ALL patients had bone mineralization defect.
14	2008	children	110	RCT	ALL treatments lead to bone turnover.
15	2008	children	200	RCT	ALL treatments lead to bone turnover.
16	2005	children	10	cohort	ALL treatments lead to bone turnover.
17	2004	children	59	cohort	ALL treatments did not increase bone turnover.
18	1999	children	28	cohort	ALL treatments lead to bone turnover.
19	1998	children	56	cohort	ALL treatments lead to bone turnover.
20	1996	children	40	cohort	ALL treatments lead to bone turnover.
21	1995	children	40	cohort	ALL treatments lead to bone turnover.

Discussion

Trace elements concentration might decline due to malabsorption or inadequate intake in children with ALL. On the other hand long term hospital stay and immobility and corticosteroid therapy in ALL patients lead to osteopenia and bone loss. It seems that osteopenia and osteonecrosis are more common in ALL and Non-Hodgkin Lymphoma (NHL). And it happens in one third of these patients. Osteopenia occurs more frequent in younger children and those who treated with higher doses of corticosteroids. Osteopenia in these patients is bilateral and multi articular in weight bearing part like hip (22). In some ALL patients osteoporosis is the only manifestation the underlying malignancy (3). Vitamin D is a crucial factor for body systems which is involved in the metabolism of tissues. Its main classic role is bone metabolism regulation and calcium homeostasis. Vitamin D deficiency might lead to rickets in children. Vitamin D level is lower in people with darker skin type, in autumn and winter and places which are located in higher latitudes. Malnutrition, increase in vitamin D exertion amount impaired vitamin D activation and resistance to 1,25-dihydroxyvitamin D (1, 25 $(OH)_2$ D) biologic effects are some causes of vitamin D insufficiency (23).

Recently the number of reports has been increased about metabolic and endocrine abnormalities in adults who had ALL and NHL in childhood. Endocrine disorder and reduction in to insulin sensitivity is happen in 20 to 50 percent of these patients. Growth retardation, Body Mass Index (BMI) abnormalities, thyroid and puberty disorders in these children influence bone mineral density. Corticosteroid administration, cytotoxic drugs and radiotherapy down regulate bone metabolism (24).

Choi showed that treatment with glucocorticoid and lower BMI are the main factors associated with osteopenia in children with malignancies. Z-score of -1 to -2 is more common in female patients with a history of cranial radiotherapy (25). Gunes revealed that 85% of the survivors of childhood ALL had bone mineralization defect in adolescence. Bone Mineral Density (BMD) and bone indexes reduce significantly during the first treatment years. Low daily calcium intake is the main cause of this problem, so prophylactic calcium and vitamin D supplement administration might be helpful in these cases. Although cholecalciferol and calcium supplementation added benefit had not been confirmed in all adult survivors of ALL (26).

It seems that bone turnover in this population is associated with age, tanner stage, gender and BMI. And bone turnover could not be used to predict Lumbar Spine-Bone Mineral Density (LS-BMD) Z-score (27). Some studies revealed that children who suffer from ALL and have lower bone mineral density of the lumbar spine are at more risk for fractures. Pamidronate is safe and effective in children with low BMD during and after chemotherapy (28).

The majority of intervention studies with dairy foods or calcium supplement in children and adolescents from different ethnic backgrounds have shown positive effects on bone mineral accretion at one or more of the sites measured (7, 23).

High-dose Methotrexate (HD-MTX) administration in children is associated with long-term side effects on bone metabolism and leads to insufficiency fractures and osteopenia (28).

Conclusion

The dietary history of children who are at more risk for fractures and osteopenia

should be screened by paying more attention to calcium and vitamin D intake.

Conflict of interests: None.

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