

LEVEL OF 25 (OH) COLECALCIFEROL (VIT-D) IN ACUTE LYMPHOBLASTIC LEUKEMIA: A META ANALYSIS

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Received : 12/10/2022
Received in revised form : 08/11/2022
Accepted : 16/11/2022

Keywords:

Acute lymphoblastic Leukaemia; 25 (OH) colecalciferol; hematological malignancies.

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DOI: 10.47009/jamp.2022.4.5.92

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2022; 4 (5); 446-449



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Abstract

Background: Acute lymphoblastic Leukaemia (ALL) is a malignant disorder of bone marrow primarily present with uncontrolled division of lymphoblast cells. The present study was carried out to evaluate and determine the relationship between 25 (OH) colecalciferol (Vit-D) in Acute Lymphoblastic Leukaemia patients. The aim is to compare serum 25 (OH) colecalciferol levels in Acute Lymphoblastic Leukaemia patients from previously reported studies. **Materials and Methods:** Meta-analysis was carried out on the findings of eight published studies that were related to serum 25 (OH) colecalciferol levels in Acute Lymphoblastic Leukaemia patients. The pooled mean for serum 25 (OH) colecalciferol was estimated by using a random-effects model. **Result:** Pooled mean for serum 25 (OH) colecalciferol was found to be decreased in Acute Lymphoblastic Leukaemia patients with I² value 21.36%. **Conclusion:** Pooled mean reported in this study can be useful in working out the management of acute lymphoblastic leukaemia along with prevention of vitamin D deficiency consequences.

INTRODUCTION

Acute lymphoblastic Leukaemia (ALL) is a malignant haematological disease primarily present with unregulated division of lymphoblast cells in bone marrow. Clinical feature associated with ALL; Generalised weakness, anaemia, headache, vomiting, neck stiffness, dizziness, pyrexia, weight loss, bone pain, joint pain, hepatomegaly and splenomegaly.^[1] Epidemiologically, the disease has increased from 49100 up to 64200 cases in an interval of 27 years from 1990 to 2017.^[2] The ALL is most common paediatric malignancy with an incidence of ¼ of all childhood cancer and ¾ of newly diagnosed cases. Increase prevalence is present among adolescent population.

Vitamin D which are known to regulate calcium absorption through calbindin and bone mineralisation; also have a potential role in cell cycle, likewise cell differentiation/maturation and immunological response.^[3]

1,25dihydroxycolecalciferol is the most, biologically active form of vitamin D, formed from hydroxylation of 25-hydroxycalciferol (calcidiol) in cells of proximal tubules catalysed by α-1 hydroxylase (a mitochondrial oxygenase) in kidney.^[4] Vitamin D acts through binding with

nuclear receptor, and regulates gene transcription.^[5] Existing studies have suggested that people having insufficient levels (10-30 ng/ml) of 25-hydroxycalciferol (circulating form of Vit-D) are more prone to certain types of cancers.^[6] Both prospective and retrospective studies have indicated, levels below 20 ng/ml generally reflects high risk for solid tumour mass, breast cancer, leukaemia and mortality from these cancers.^[7]

Classification of Acute lymphoblastic Leukaemia: Back in 1976 Bennett et al. under French-American British (FAB) have classified ALL into three sub categories L1,L2,L3 on the basis of morphological appearance; nucleus to cytoplasmic ratio (N/C), Nucleolus; presence, prominence, frequency; Nuclear membrane appearance.^[8] The world health organisation in 1997, proposed blended classification for cytogenetic and morphological features of leukemic blast cells (ALL): B-Lymphoblastic, T-Lymphoblastic and Burkitt-cell Leukaemia. Later on Burkitt cell Leukaemia was removed from classification because it has same entity as that of Burkitt lymphoma. Finally B-Lymphoblastic Leukaemia was divided into two sub-categories; B-Lymphoblastic Leukaemia with

repetitive genetic anomaly and B-ALL not specified.^[2]

Pathology and Genetic Basis behind Acute Lymphoblastic Leukaemia

The pathogenesis of ALL include uncontrolled division of progenitor lymphoid cells resulted from developmental arrest at point of differentiation.^[10] The blast cells then continue to infiltrate reticuloendothelial system including bone marrow, and other extramedullary sites leads to enlargement of spleen, lymph node and liver in 20% cases.^[11] There are several environmental factors like pesticide exposure, ionising radiations, solvent exposure, viral insertion include Epstein-barr virus and Human immunodeficiency virus etc, and genetic abnormalities include chromosomal, gene translocation, mutation; deletion, kinase activation.^[12] These translocation are (9;22) BCR-ABL1, (12;21) ETV6-RUNX1, (1;19) TCF3-PBX1 are the reordered form of Mixed linkage Leukaemia (MLL).^[13] Mullighan GC et al. have also shown that more than 80% of subjects are linked with the deletion of transcription factors include IKROS family zinc finger 1, early B cell factor 1 (EBF-1), transcription factor-2 (E2A) and paired box 5 (PBX5).^[14] Likewise, kinase active mutation are also seen in 90% of Ph like Acute lymphoblastic Leukaemia. ABL1, JAK2, PDGFRB, CLRF2 and EPOR, activating mutation of ILR7 and FLT3 and deletion of SH2B3 which encodes JAK2-negative regulator LNK, are the most commonly occurring rearrangements.^[4]

Several studies have been conducted in different regions, which shows varying estimate of the average 25 (OH) colecalciferol (Vit-D) measure with standard deviation among patients Acute Lymphoblastic Leukemia as highlights in [Table 1] of this study. These results mislead the clinician in decision of the actual measure of the respective parameters i.e., there is lack of systematic review of this major health issue. Hence, the present study was carried out to evaluate and determine the relationship between serum 25 (OH) colecalciferol values in Acute Lymphoblastic leukemia.

MATERIALS AND METHODS

We carried out a meta-analysis of the heterogenic data of Acute Lymphoblastic Leukemia from published studies. Guidelines for the Meta-Analyses was accordance to PRISMA Statement. 15

Search Method

We searched for articles which were published in English from January 2001 to November 2020 by using PubMed. Keywords used for searching were: “Acute Lymphoblastic Leukemia” and “serum 25-Hydroxycholecalciferol” OR “Vitamin D” The study selection processes is summarized in [Figure 1].

Data extraction

Basic information like name of 1st author, publication year of the study, population of Patients mean and 95% CIs 25-Hydroxycholecalciferol were extracted by authors worked from each study Statistical analysis: STATA-16 statistical software was used for Statistical analysis. Model used for analysis was Random-effects model because data which was used in the study was random. The Cochran’s Q test and I2 were used to identify heterogeneity. The value I2 of 0-50% indicated insignificant heterogeneity. Bias of the publication was assessed by using the funnel plot. The summary statistical estimates, 95% confidence intervals and relative weights represented by Forest plots.

RESULTS

We included eight articles in our study that fulfil the eligibility criteria and allocated with the relationship of acute lymphoblastic leukemia with Serum 25-hydroxyvitamin D were included in the study. [Table 1] summarizes the year, place, mean and SD of Serum 25-hydroxyvitamin D. Table1. Study Characteristics for Serum 25-hydroxyvitamin D measure among acute lymphoblastic leukemia.

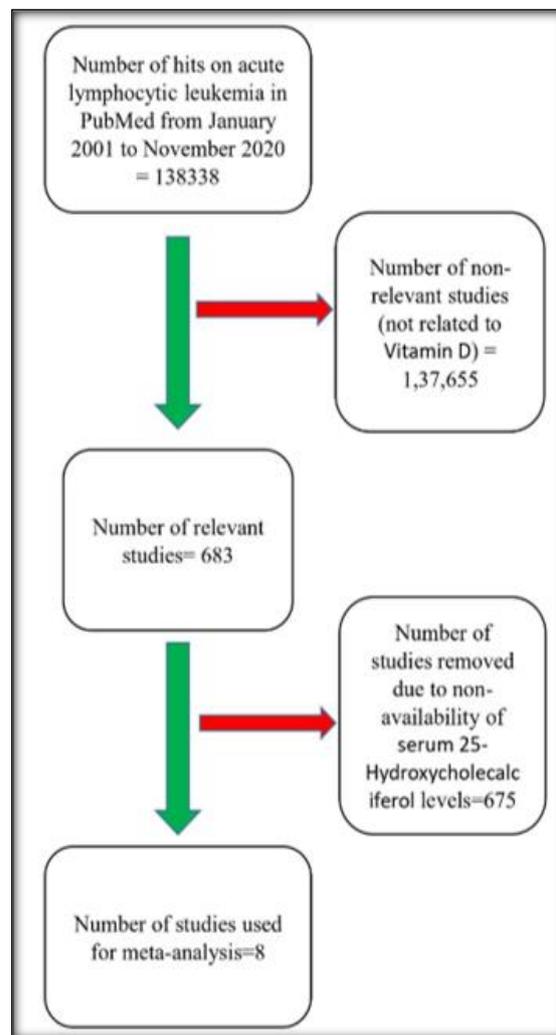


Figure 1: Flow chart in the process of study selection

Table 1: Literature Review

S. No.	Author, year	Place	Population	Mean	SD
1	Jackmann N et. al. 2019(Jackmann et al., 2020)	Sweden	295	24.28	9.32
2	Delvin E et. al. 2018(Delvin et al., 2019)	Canada	124	22.80	7.65
3	Akhgarjand C et. al. 2018(Akhgarjand et al., 2018)	Iran	30	21.80	2.36
4	Modan-Moses D et. al. 2012(Modan-Moses et al., 2012)	Israel	40	17.00	2.40
5	Gunes AM et. al. 2010(Gunes et al., 2010)	Turkey	66	21.04	7.85
6	Wiernikowski JT et. al. 2005 (Wiernikowski et al., 2005)	Canada	10	25.37	5.26
7	Thomas X et. al. 2013(Thomas et al., 2011)	France	105	22.90	10.50
8	Simmons JH et. al. 2012 (Simmons et al., 2011)	U.SA	52	26.00	3.67

Serum 25-hydroxyvitamin D reported in all eight studies dealing with its relationship with acute lymphoblastic leukemia. Overall mean of all studies was 21.59 ng/ml (95% CI: 18.14-25.03) with $I^2 = 21.36\%$ which shows homogeneity in all studies as shown in [Figure 2A].

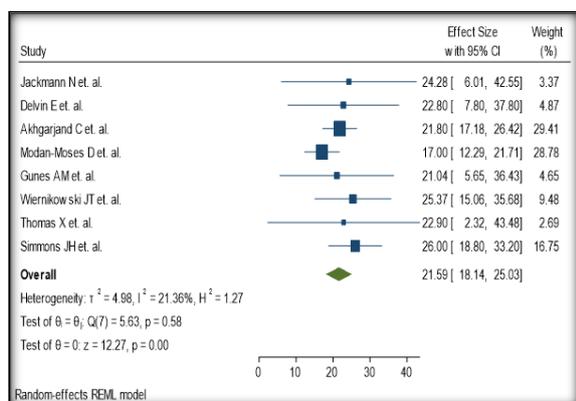


Figure 2A: Forest plot of random-effects meta-analysis for Serum 25-hydroxyvitamin D in acute lymphoblastic Leukaemia.

Research publication bias was small because all studies were present nearby and inside of the funnel figure as shown in [Figure 2B].

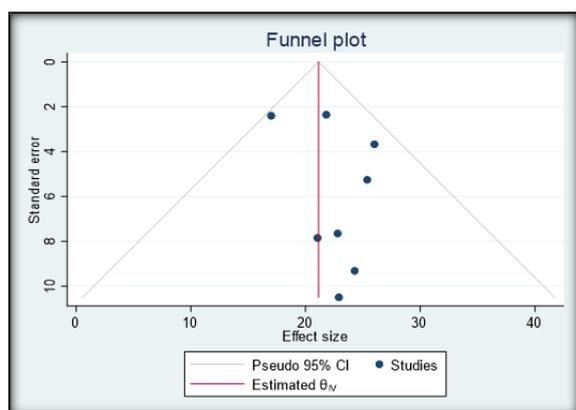


Figure 2B: Funnel plot with Pseudo 95% Confidence Interval for Serum 25-hydroxyvitamin D in acute lymphoblastic Leukemia.

DISCUSSION

This meta-analysis work evaluating the relationship between serum vitamin D and acute lymphoblastic leukemia. Total 08 studies of acute lymphoblastic leukemia were taken in the study. This study used a

random effect model, with the assumption that each study used randomly selected samples for analysis. The high heterogeneity observed in the studies of each variable type was due to the different periods in which the studies were carried out, and the diversity of locations, cultures and economic status. Human body maintained Normal mineral regulation in the bones is by for regulating the 1, 25 (OH) 2D secretion. Two decades ago, scientists wrote about the immune response modulation of that 1, 25 (OH) 2D suppresses proliferation, immunoglobulin production, inhibits the adaptive immune response, and delays B cell precursor's differentiation into plasma cells And also triggered peptide expression of antimicrobial activity in myeloid and epithelial cells.^[15,16,17] There are three main pathological processes which were related to Presentations of acute Leukemia. These are marrow failure due to extensive infiltration by blast cells, infiltration of other tissues by blasts, and systemic effects of cytokines released by tumour cells. Whenever a child presents with classical signs of anemia, thrombocytopenia, and pronounced hepatosplenomegaly or lymphadenopathy always have strongly chance of Leukaemia.^[11] This study reveals that pooled mean acute lymphoblastic leukemia patients had low Serum 25-hydroxyvitamin D levels. These were confirm by many studies.^[7,18,19,20] The possible mechanism was that status of Vitamin D could be effected by many environmental factors like diet and seasonal variation in sun exposure) than to a specific cancer-related defect in vitamin D metabolism. Even though malabsorption of dietary vitamin D also occur due to chemotherapy-induced intestinal mucositis.^[21,22]

CONCLUSION

Study has reported pooled mean for 25 (OH) colecalciferol levels in Acute Lymphoblastic Leukemia patients and found that there were deficiency of 25(OH)D in Acute Lymphoblastic Leukemia patients. Moreover, these results suggest that routinely quantification valuation of serum 25 (OH) colecalciferol will help in the management of Acute Lymphoblastic Leukemia.

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