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EFFECT OF INDUCTION CHEMOTHERAPY ON VITAMIN D LEVEL IN CHILDREN WITH ACUTE LEUKEMIA

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ABSTRACT: Background: Subnormal level of vitamin D are associated with the higher frequency of cancer and correlated with inferior prognosis in some cancers; no data exist for acute leukemia. **Aim of the work:** To clarify the relationship between serum vitamin D levels and acute leukemia in children. **Materials and Methods:** Vitamin D level was measured in sixty-six pediatric patients who are newly diagnosed with acute leukemia in Central Child Teaching Hospital during a period between March 5th to August 30th, 2017 and normal 50 children were considered as the control group. Information on the patients were obtained from the medical files of the patients. Patients were classified on a random base as active patients group how the received daily requirement of vitamin D during induction chemotherapy period and passive patients' group who were treated with chemotherapy only. Vitamin D level was reassessed at the time of remission. **Results:** The serum vitamin D level in children with acute leukemia was below normal ranges; at the time of diagnosis, the mean of serum level was 13 ng/dl, while in the control group was 21 ng/dl. There was a statistical difference between the patient's group and the control group (p-value 0.001). At the time of remission, serum vitamin D level decreased to 11.8 ng/dl in the passive patients' group and increased in active patients group to 17.1 ng/dl. **Conclusion:** vitamin D level was low in a majority of pediatric patients with acute leukemia, and it was further reduced after induction-remission in patients without vitamin D replacement.

INTRODUCTION: It is well known that vitamin D is involved in many roles and integrated into the function of many tissues nowadays. This was justified by the discovery of the receptors for vitamin D in most of the body tissues. These receptors are labeled as vitamin D receptors (VDR) [1, 2].

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To date, there are two forms of vitamin D; Calcitriol (D3) which is a derivative of 7-dehydrocholesterol by the effect ultraviolet light, and Ergocalciferol (D2) which is derived from the plant sterol ergosterol. The VDR is a transcription factor that binds to DNA, which in turn, called vitamin D response elements (VDREs) [3].

Normal mineral regulation in the bones is maintained by the body's ability for regulating 1, 25 (OH) 2D secretion [4]. Twenty-five years ago, scientists wrote about the immune response modulation of 1, 25 (OH) 2D [5]. It inhibits the adaptive immune response, suppresses proliferation, immunoglobulin production and delays B cell

precursor's differentiation into plasma cells [6]. The antimicrobial peptide expression is triggered by 1, 25 (OH) 2D in myeloid and epithelial cells, and in turn, both macrophages and epithelial cells produce 1, 25 (OH) 2D [7]. Acute Lymphoblastic Leukemia (ALL) is a malignant disorder of lymphocyte progenitors. The advances in the treatment using multi-agents' therapies and risk stratification based on the biology of the cells and assessment of early treatment efficacy had led to increasing the survival of childhood ALL to more than 80% in centers of excellence [8]. On the other hand, Acute Myeloid Leukemia (AML) accounts for 25% of childhood leukemia cases; its outcome has also improved nowadays to reach a survival rate of more than 65% [9].

They have been few studies discussing the relationship between the level of vitamin D, which is variable changes from 8 - 12 ng/ml from the mean in people during seasons, and the increased rate of acute leukemia in these seasons [10]. Vitamin D deficiency historically has been defined as a blood level of 25hydroxyVitaminD below 10 ng/dl. There is a scientific debate about the optimal vitamin D blood level. Current practice in the UK, as recommended by the British Paediatric and Adolescent Bone Group, is to continue to use that as the defined level of deficiency, and to define 'insufficiency' as between 10 and 20 ng/dl. Some laboratories and authorities use higher levels, but this current practice is based on robust evidence of benefits to bone health when levels are more than 30 ng/dl [11]. This study is aimed to detect the role of chemotherapy on serum vitamin D levels in children with acute leukemia.

Patients and Method: In this therapeutic study, sixty-six pediatric patients were diagnosed with acute leukemia in Central Child Teaching Hospital in Baghdad during the period between March 5th and August 30th, 2017. The patients were admitted to the hematology ward for induction chemotherapy treatment. Information of the patients regarding demography was obtained from the available medical record file system of the hospital. Another normal fifty children were considered as a control group. Diagnosis of acute leukemia was based on suspicious clinical features, complete blood count and film, and bone marrow aspiration examination. Acute leukemia was considered when the blast cells more or equals 25 % in the bone marrow [12]. Remission is defined as blasts less than 5% of the bone marrow by normal hematopoietic renewal [13].

The differentiation between ALL and AML was based on the FAB classification, which was decided by the lab hematopathologist. Investigations were done to the patients as baseline workup (as complete blood count, liver function test and renal function test) as well as bone marrow aspiration examination. All these investigations' results were recorded form medical reports of the patients. The investigations were done to all patients at a time of diagnosis, weekly for some of them, as well as at the time of remission. Estimation of serum 25 (OH) D, serum calcium and serum phosphorus were done for all patients and for control who were enrolled in the study.

The study sample included all newly diagnosed cases of pediatric acute leukemia below the age of 14; verbal consent was obtained from the guardian (mother or the companion). The study excluded patients with renal or hepatic impairment, patients on antiepileptic therapy, families refused to receive chemotherapy or refused to be enrolled in the study or those who were discharged from the hospital on their responsibility.

The study sample was divided into two groups; the active group who received daily prophylactic vitamin D dose. Those patients were randomized on the base that "patients diagnosed on Sundays, Tuesdays, and Thursdays were considered as an active group" while "patients diagnosed in the other days of the week" were enrolled as the passive group. The active group was thirty-four, twenty-seven patients were diagnosed with ALL, while seven were diagnosed with AML. Those patients received a single daily dose of vitamin D (800 IU per day) as drops or capsules in the morning under the supervision of the responsible physician along with the scheduled chemotherapy protocol assigned for their disease. The passive group (thirty-two participants) received no vitamin D but only their assigned chemotherapy.

For all participants, active and passive groups, serum levels of 25 (OH) D, serum calcium, and serum phosphorus were measured at the time of

diagnosis. Second serum levels were measured at time remission (day 30 of treatment) except one patient in the active group with AML who didn't achieve remission after first induction chemotherapy and his measurement was delayed till he got remission and nine patients in the passive group who did not get remission state (two of them died, five were lost, and two were treated in another center). Quantitative 25-Hydroxy Vitamin D, serum calcium, and serum phosphorus were determined by using one-step delayed chemiluminescent microparticle immunoassay [Roche Diagnostics (Germany)].

Statistical analysis was carried out using the statistical package for the social science software package, version 20.0 (IBM Corporation, Chicago, USA); Data were showed as a median for numeric data and percentiles for non-numeric data. A non-paired t-test was used to test a significant difference between the cases of both types of acute leukemia and a paired t-test was used to test the significant difference between levels of vitamin D at induction and remission. P values less than 0.05 were considered statistically significant.

RESULTS: In the study group, table one shows the age and laboratory finding in patients and control group; females constituted (51.5%) of the total number while males were (48.5%). In the control group, females were (54%) while males were (46%), with no significant statistical difference. Measuring vitamin D levels in both groups (patients at diagnosis and control) had yielded a significant statistical difference between both groups. The level tends to be lower in patients (Mean of 13.0 ng/ml in patients and 21 ng/ml in control), with a P-value of (0.001). The same results have been shown with measuring serum Calcium and serum Phosphorus level for both (patients at diagnosis and control), the level was lower in patients than the control group (8.72 mg/dl *vs.* 9.59 mg/dl for Calcium, and 4.58 mg/dl *vs.* 4.92 mg/dl for Phosphorus level in patients and control respectively. The difference was significant statistically (0.01 for Calcium and 0.04 for Phosphorus) Fifty percent of active patients were female, and fifty percent were male. For the passive group, 17 patients (53.1%) of them were female, while 15 patients were male (46.9%), with no statistical significance difference (P value 0.4). ALL was diagnosed in 27 active patients (79.4%), while AML was diagnosed in seven active patients (20.6%). In the passive participant group, ALL were diagnosed in twenty-six patients (81.2%), while AML was diagnosed in six patients (18.8%). The correlation was not significant statistically (P-value 0.5), as shown in **Table 2**.

TABLE 1: LEVELS OF VITAMIN D, CALCIUM AND PHOSPHORUS AMONG PATIENTS AND CONTROL GROUPS

Variable	Patients			Control			P value
	Mean	N	SD	Mean	N	SD	
Vit D (ng/dl)	13.0	66	7.17	21	50	4.1	0.001
Calcium mg/dl	8.72	66	1.43	9.59	50	0.63	0.01
Phosphorus mg/dl	4.58	66	1.0	4.92	50	0.6	0.04

TABLE 2: DISTRIBUTION OF GENDER AND TYPE OF LEUKEMIA IN ALL PATIENTS

Item	Active (%)	Passive (%)	Total	P value
Gender				
Males	17 (50)	15 (46.9)	32	
Females	17 (50)	17 (53.1)	34	0.4
Total	34 (100)	32 (100)	66	
Type of Leukemia				
ALL	27 (79.4)	26 (81.2)	53	
AML	7 (20.6)	6 (18.8)	13	0.5
Total	34 (100)	32 (100)	66	

Baseline investigations for both groups were recorded from the file of the patients; no statistically significant differences in the results of CBC, liver function and renal function were noted at both times (diagnosis and remission) as shown in **Table 3**.

TABLE 3: OTHER HEMATOLOGICAL AND BIOCHEMICAL DATA OF THE ACTIVE AND PASSIVE PATIENTS

Item	Active			Passive			P value
	Mean	N	SD	Mean	N	SD	
Age (years)	7.0	34	3.66	5.2	32	3.0	0.03
At diagnosis							
Hb level g/dl	7.6	34	1.8	7.6	32	1.8	0.9
WBC count cmm(*1000)	25.6	34	40.7	15.0	32	13.0	0.1
Platelet count cmm (*1000)	45.7	34	35.8	47.1	32	43.1	0.8
Blood urea mg/dl	25.5	34	7.1	29.2	32	11.2	0.1
Serum creatinine mg/dl	0.5	25	0.2	0.5	20	0.3	0.7
Serum bilirubin mg/dl	0.6	34	0.3	0.7	32	0.2	0.5
Serum GOT mg/dl	28.1	34	16.9	27.4	32	20.4	0.8
Serum GPT mg/dl	33.0	34	22.2	50.2	32	71.4	0.1
Alkaline phosphatase	136.6	34	46.7	139.8	32	42.9	0.7
At remission							
Hb level g/dl	10.9	34	1.4	10.8	23	1.4	0.9
WBC count cmm(*1000)	6.3	34	3.7	6.9	23	3.3	0.5
Platelet count cmm (*1000)	19.4	34	10.2	21.1	23	9.1	0.5
Blood urea mg/dl	31.1	34	26.0	32.9	23	11.0	0.7
Serum creatinine mg/dl	0.58	34	0.19	0.4	23	0.16	0.1
Serum bilirubin mg/dl	0.92	34	0.4	1.2	23	0.7	0.3
Serum GOT mg/dl	32	34	21	41	23	26	0.16
Serum GPT mg/dl	28.2	34	17	45	23	60	0.14
Alkaline phosphatase	85.3	34	32	98	23	42	0.2

Analysis of each group according to time (diagnosis versus remission) have shown the following results: for passive patients' group, serum vitamin D level at diagnosis was 13.7 ng/dl, which was higher than the level in remission state, 11.8 ng/dl, with a significant difference, P-value 0.007. For the active group of patients, it was shown that the serum level of vitamin D at the time of diagnosis (12.2 ng/dl) while it was lower than that recorded at remission (17.1 ng/dl), with a significant statistical difference (P value 0.001), as shown in **Table 4**.

TABLE 4: MEAN LEVELS OF 25(OH) D ng/ml IN PASSIVE AND ACTIVE PATIENTS AT DIAGNOSIS AND REMISSION

Time	Mean	N	SD	P-value
Passive participants				
Diagnosis	13.7	32	7.0	0.007
Remission	11.8	23	5.7	
Active Participants				
Diagnosis	12.2	34	7.6	0.001
Remission	17.1	34	8.5	

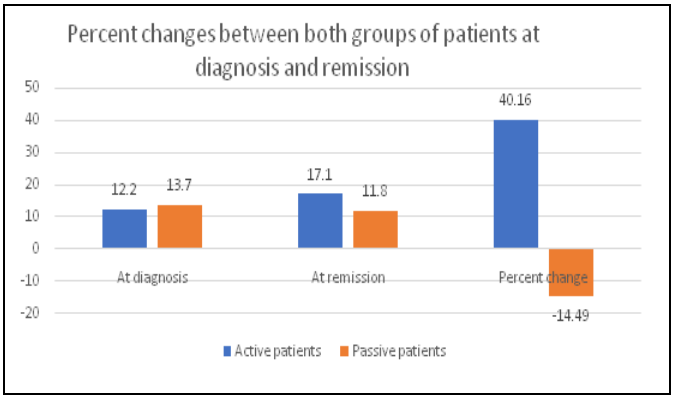

FIG. 1: PERCENT CHANGES BETWEEN BOTH GROUPS OF PATIENTS AT DIAGNOSIS AND REMISSION

The level of vitamin D in active patients group increased at remission as compared to the level at diagnosis. This increment still below that reported in the control group, while in the passive patient's group, there was a decrease in the level of vitamin D at remission if compared to the level of the vitamin at the time of diagnosis. The percent change is 40.16% for the active participants and -14.49% for the passive participants, as shown in **Fig. 1**.

DISCUSSION: The mean level of vitamin D, which recorded in healthy children, was 21 ng/dl. According to guidelines report, this level is considered normal but in the lower limit. 14 Hypovitaminosis D state was recorded in many areas all over the world; even the ordinary healthy

people may have a state of hypovitaminosis. Regarding children and adolescents in the middle east, many studies reported mean vitamin D levels of 10-20 ng/ml, revealing a large proportion of healthy children (30-75%) have vitamin D levels below the deemed desirable cut-off [15].

The difference in the serum level of vitamin D between normal control and both patients' group with acute leukemia was statistically significant; the mean level of vitamin D is low in patients with acute leukemia. Many studies have confirmed that the level of vitamin in patients with acute leukemia is less than normal. Arshi Naz study from Pakistan showed that vitamin D level was subnormal in a majority of patients with acute leukemia [16].

Tahani A. study from Egypt proved that there is a significantly lower vitamin D level in acute leukemia patients than the control group [17]. A study in (UAE) documented that acute leukemia was common among adult females than adult males, despite the real fact that the population of the UAE consists of more men than women, and acute leukemia is widely known to be more common in men. The hypothesis was that the women have less sunlight exposure, because of their conservative clothing, which may play the role of their higher incidence of acute leukemia [18].

In both patient's groups, there was no difference in serum level regarding gender and leukemia types which is compatible with the study from Egypt which showed no difference in the serum level of vitamin D between both genders in acute leukemia at diagnosis time [16]. Despite the lack of research sources that discuss the difference in the level of vitamin D in both types of acute leukemia in children, the decrease in the level of the vitamin D was mentioned in a study from Pakistan which indicated that this decline was seen in both types without the statistical significance [15]. 'The increment in the level of vitamin D at the end of the induction period was statistically significant (P-value 0.001). These findings are compatible with a recent study published using the therapeutic dose of vitamin D 50000 IU weekly given to the adult patient with lymphoma or chronic lymphoblastic leukemia for 12 weeks; there was increasing in vitamin D level from 17 ng/dl to 54 ng/dl as mean [19].

For passive patients' group (the patients treated with only chemotherapy according to leukemia types) at the remission state, the mean level of serum vitamin D was 11.8 ng/dl which is less than the serum level of the same patients at a time of diagnosis, (P-value 0.007). Sfeir from the USA showed decrement of vitamin D level from 34 ng/dl to 32 ng/dl after 12-week treatment [19]. Lowering of vitamin D level can be explained by many theories, as low oral intake, impaired gastrointestinal absorption due to disease and deficient exposure to sunlight during hospitalization. All these may increase the existing deficiency. Additionally, there is low information on the practice of supplementation during hospital admission. Also, the dilution effect of fluid supplementation during hospitalization may reflect the lower vitamin D concentrations. This may be explained why the prevalence of vitamin D deficiency in hospitalized individuals is well documented [20].

CONCLUSION: Vitamin D level was subnormal in a majority of pediatric patients with acute leukemia. It was further reduced after remission-induction in patients without vitamin D replacement. However, the level was increased after remission-induction in patients with vitamin D replacement.

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