Original Article

Vitamin D Deficiency in Chronic Lymphocytic Leukaemia: Makurdi Perspective

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ABSTRACT

Vitamin D is a group of fat-soluble vitamins, commonly known for its critical role in calcium homeostasis and bone mineralization, but more recently it has been implicated in the pathogenesis of hematological cancers and shows promise as an anti-cancer therapy. Serum Vitamin D level has a positive relation with rate of disease progression in Chronic Lymphocytic Leukemia (CLL) and as such Vitamin D deficiency is a poor prognostic factor. This study is designed to evaluate the serum vitamin D concentration in CLL participants in comparison to age-matched non CLL participants. This was a cross-sectional study carried out among CLL patients seeking care in Benue state University Teaching Hospital. Thirty-six CLL patients and 36 healthy age and sex matched controls were recruited for the study. Their Full Blood Count and serum vitamin D levels were determined. Data obtained from the study were analysed using Statistical Package for Social Sciences (SPSS) version 23.0. The concentration of serum vitamin D in the CLL group was significantly lower than that of control. Prevalence of vitamin D deficiency was commoner in the CLL group (52.8%, n=19) compared to controls (5.6%, n=2), P <0.05. There was no correlation between serum Vitamin D and age, Rai stage, neutrophil count, lymphocyte count and haematocrit. However, a negative correlation was found between serum vitamin D and platelet count.There is a high prevalence of Vitamin D deficiency among CLL patients in Makurdi, Benue state. Though this deficiency does not correlate with the Rai stage of the disease. Therefore, serum vitamin D assay should be part of routine investigation done at diagnosis of CLL so that its deficiency can be corrected early.

Keywords: Chronic lymphocytic leukaemia (CLL), Vitamin D

INTRODUCTION

Vitamin D is a group of fat-soluble vitamins, commonly known for its critical role in calcium homeostasis and bone mineralization, more recently vitamin D has been implicated in hematological cancer pathogenesis and shows promise as an anti-cancer therapy[1]. In humans, Vitamin D (calciferol) is photochemically synthesized from its precursor 7-dehydrocholesterol in the skin under the influence of solar ultraviolet B (UVB) radiation in form of Vitamin D3 (cholecalciferol), although the vitamin can also be obtained through dietary sources in form of Vitamin D2 (ergocalciferol)[2]. Both Vitamin D3 and D2 isoforms are subsequently metabolized to 25-hydroxyvitamin D in the liver by 25-hydroxylase. The 25(OH)D (calcidiol) is bound mostly (85-95%) on Vitamin D-binding protein (VDBP), partly (5-15%) on albumin, while few (<1%) remain free in plasma and reflects both cutaneous synthesis and

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dietary acquisition of the Vitamin[2]. In the proximal renal tubules, the inactive form is further metabolized to the more physiologically active 1,25-dihydroxyvitamin D [1,25(OH)2D or calcitriol], an active endocrine hormone, by 1-alpha-hydroxylase[2]. The regulation of the active Vitamin D is under the tight regulatory control of calcium and parathyroid hormone (PTH)[2].

Chronic Lymphocytic Leukaemia (CLL) is a clonal malignancy of the lymphoid system in which there is increased proliferation and accumulation of mature-looking lymphocytes in the blood and bone marrow[3]. It is the commonest leukaemia in adults in the Western World[3]. It is commoner in males and has a peak incidence in the seventh decade[3]. Though the incidence in Nigeria has not been ascertained, it is the most prevalent leukaemia in adults in our environment, as shown in studies carried out by Onoja *et al.,*[4] and Nwannadi *et al.,*[5] in North- central and south-south of Nigeria.

The aetiology is not known but risk factors for developing CLL include: exposure to ionizing radiation, exposure to petrochemicals, familial tendencies, and exposure to agrochemicals[6].

The diagnosis of CLL is based on both clinical and laboratory features of the disease. The clinical features include symptoms due to anaemia, immunosuppression, organomegaly and thrombocytopaenia, while the laboratory features include; persistent lymphocytosis, mature-looking lymphocytes and smudge cells on blood film, characteristic immunophenotype and genotype of the malignant cells[7].

The management of CLL is dependent on the age, performance status of the patient, the stage and the biology of the disease. These comprise of watchful waiting for the indolent and early-stage disease while chemo-immunotherapy is used in the advanced disease. Disease-related symptoms, toxic effects of therapy, and the awareness of living with an incurable disease can have a profound impact on health-related quality of life[8].

Calcitriol is the biologically active form of vitamin D which modulates a plethora of cellular processes following its receptor ligation, namely the vitamin D receptor (VDR)[9]. The autocrine and paracrine effects of vitamin D metabolism include maintaining regulation of cell proliferation, apoptosis induction, immunomodulation and increased cell differentiation signals[10]. Calcitriol activity against metastasis has been demonstrated in various tumor models, including cancers of the lung, bone, colon, kidney, breast and prostate[10]. Furthermore, evidence of an effect of 1,25(OH)D on lymphoma cells in particular has been demonstrated both in the laboratory, with observed promotion of differentiation and antiproliferative effects on a variety of lymphoma cells line in vitro, and in an early study demonstrating tumor response to alfa-calcidol in low grade follicular and small-cleaved cell lymphoma[10].

It has been proposed that vitamin D may play a role in prevention and treatment of cancer while epidemiological studies have linked vitamin D insufficiency to adverse disease outcomes in various B cell malignancies, including chronic lymphocytic leukemia (CLL)[9]. Interestingly, it has also been documented that vitamin D replenishment in CLL patients, including those undergoing chemotherapy, is safe and effective in restoring vitamin D levels which may improve the quality of life and performance status of the patient[9]. This study therefore was designed to evaluate the serum vitamin D concentration of CLL participants and to compare them with results from age-matched non CLL participants.

MATERIALS AND METHODS

This was a cross-sectional study that lasted for 12months (from October 2018 to October 2019). The participants were recruited from the Haematology Outpatient Clinic (HOPC). Participants were recruited sequentially from consenting chronic lymphocytic leukaemia patients who met the inclusion criteria (study group), and the control group comprised apparently healthy members of staff of BSUTH and blood donors at BSUTH.

The inclusion criteria were:

- Consenting CLL patients.
- Healthy consenting members of staff and

blood donors at BSUTH, whose blood films were not suggestive of CLL.

Exclusion Criteria:

- CLL patients on Vitamin D replacement.
- Patients on multivitamin supplementation
- Controls on multivitamin supplementation
- Non-consenting individuals
- Controls with non-optimal haemogram

Sample Size Determination

The sample size was determined by the number of CLL patients that presented to the haematology clinic during the time frame of the study which was 12 months.

Sampling Technique

Purposive sampling was used as sampling technique and all the patients that presented during the study period and met the inclusion criteria were recruited.

Ethical Considerations:

Ethical approval was obtained from the Health Research Ethics Committee of the Benue State University Teaching Hospital (BSUTH), Makurdi Ethical Review Board (BSUTH/MKD/HREC/2018B/2018/0006). The right of confidentiality and anonymity of each participant was protected all through the study. Consent was sought and obtained in writing from each participant.

Beneficence to the Participants:

This study evaluated the serum vitamin D concentration, full blood count and peripheral blood film of both study and control groups at no cost to the participants. This was used to classify them into groups of individuals that have adequate and subnormal or deficient serum levels of serum vitamin D. The prevalence of vitamin D deficiency among CLL and normal participants was determined from this study. No financial incentive was given to the participants.

Risks to the Participants:

This study involved collection of 7ml of venous blood for various investigations which caused mild discomfort. The participant had the right to decline as participation was voluntary.

Sample Collection:

Blood sample was collected in Potassium Ethylene Diamine Tetraacetic Acid (KEDTA) and plain bottles after overnight fast. The sample in EDTA was used for Full Blood Count (FBC), peripheral blood film and reticulocyte count. The blood in plain bottle was allowed to stand for a minimum of two hours to clot and retract. The retracted sample was centrifuged at 2000g for 20 minutes after which serum was decanted and stored at -20^{0}C till the time for vitamin D analysis.

Laboratory Analysis:

Serum Vitamin D assay

This was done using an Enzyme-linked Immunosorbent Assay (ELISA) test for serum Vitamin D analysis Vitamin level less than 30 ng/mL was taken to be vitamin D deficiency.

Full Blood Count (FBC)

The FBC parameters were analyzed using a Sysmex KX-21 3 part auto-analyzer[13].

Data Analysis:

Data obtained from the study were subjected to statistical analysis using computer software program SPSS version 23 (statistical package for social science version 23). The continuous variables were expressed as mean $\pm$ standard deviation. Paired samples' t-test was used to compare the mean of haematological indices and serum vitamin D of the CLL and Control group, while Chi-square test and Wilcoxon signed rank were used for ordinal data. The statistically significant level was set at $p < 0.05$.

RESULTS

A total of 72 participants who met the inclusion criteria were recruited into this study.

Table 1 shows the age and sex distribution of the participants. In the CLL group, 13.9% (n=10) were less than 50years while half (n=36, 50%) of the participants were more than 60years, a third (33.3%, n=24) were male while 66.7% (n=48) were female.

The Rai staging of the participants is as shown in

table 2. Majority of the patients were on stage III (36.1%, n=26) and IV(38.9%, n=28) while the rest were on stage I(19.4%, n=14)and II(5.6%, n=4).

The haematological indices of CLL participants and control participants are shown in table 3. The mean ± SD of total white cell count of CLL participants was 66.48 ± 66.35 x10^9 /L while that of controls was 5.6 ± 1.3 x 10^9/L with p= 0.000. The mean ± SD of haemoglobin concentration of CLL participants was 9.14 ± 2.02 g/dl while that of controls was 13.8 ± 1.7 with p= 0.000. The serum vitamin D concentration of CLL participants was 32.08 ± 14.14ng/ml while that of control was 49.06 ± 18.82 with p=0.000.

Figure 1 shows the distribution of vitamin D deficiency among CLL and control participants. Only Two (5.6%) of the control participants were vitamin D deficient while a little more than half (52.8%) of CLL participants were found to be deficient of vitamin D.

As shown in table 4 the mean serum vitamin D for intermediate risk (Rai I and II) are 30.15 ± 8.62 while for high risk disease (Rai III and IV) it is 32.14 ± 12.23 with p= 0.32

Figure 2 shows the distribution of CLL participants into risk categories. A quarter (25%, n=9)of the participants had intermediate risk while three quarters (75%, n=27) had high risk disease.

The correlation coefficient between serum vitamin D and Rai stage, age, haematocrit, lymphocyte, platelet count, neutrophil count is shown in table 5 and all are not statistically significant (p>0.05) except for platelets which had a significant negative correlation.

Table 1: Age and sex distribution of the study participants

Age distribution of study participants		
Age group(years)	CLL frequency n(%)	Control frequency n(%)
41-50	5(13.9)	12(33.3)
51-60	13(36.1)	13(36.1)
61-70	12(33.3)	8(22.2)
≥71	6(16.7)	3(8.3)
Total	100	100
Sex distribution of participants		
Sex	CLL n (%)	Control n(%)
Male	12(33.3)	18(50)
Female	24(66.7)	18(50)
Male: Female Ratio	1:2	1:1

Table 2: Rai staging of CLL participants

Stage (risk category)	Frequency n	Frequency %
I (intermediate risk)	7	19.4
II(intermediate risk)	2	5.6
III(high risk)	13	36.1
IV(high risk)	14	38.9
Total	36	100

Table 3: Blood parameters of Control and CLL participants

Variable	Control (mean ± SD)	CLL (mean ± SD)	p-value
+T WBC(x 10^9 /L)	5.63 ± 1.26	66.48 ± 6.35	0.000*
Neutrophil count(x 10^9 /L)	2.51 ± .98	6.23 ± 4.84	0.001*
Lymphocyte count(x 10^9 /L)	2.75 ± .71	58.18 ± 9.64	0.000*
HB concentration (g/dl)	13.81 ± 1.70	9.14 ± 2.02	0.000*
Haematocrit (%)	41.75 ± 5.02	37.80 ±5.02	0.000*
Platelet count(x 10^9 /L)	194 ± 64	135 ± 25	0.002*
Serum vitamin D (ng/ml)	49.06 ± 18.82	32.08 ± 4.12	0.000*

+TWBC- Total white blood cell count, *significant at p< 0.05

Table 4. Comparison of serum vitamin D across Rai stage of CLL Participants

Stage (risk category)	Serum Vitamin D Mean ± SD (ng/ml)	F	P
I and 2 (intermediate risk)s	30.15 ± 8.62	1.20	0.32
III and IV (high risk)	32.14 ± 12.23		

*significant at p< 0.05

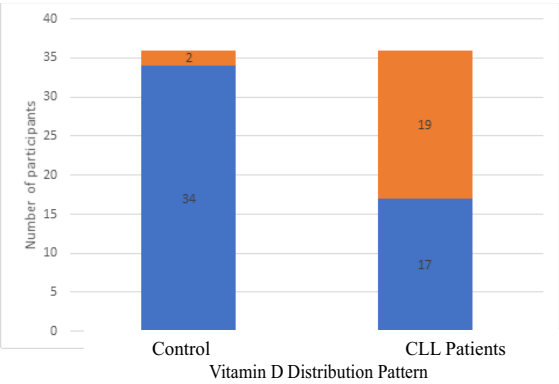

Figure 1: Frequency of Vitamin D deficiency in the control and CLL group

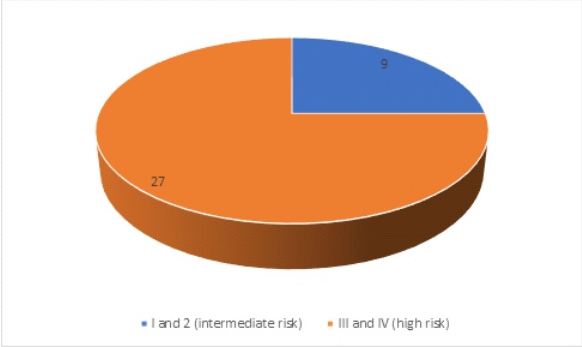

Figure 2. Distribution pattern of the risk groups of CLL patients

Table 5: Correlation between serum Vitamin D, Rai stage, Age, Neutrophil count, Lymphocyte count, Platelet count and Haematocrit in CLL Participants

Variable	Spearman's correlation	p-value
Serum Vitamin D /Rai stage	0.146	0.394
Serum Vitamin D/Age	0.159	0.354
Serum Vitamin D /Neutrophil count	-0.180	0.293
Serum Vitamin D/Lymphocyte count	-0.194	0.257
Serum Vitamin D/Haematocrit	0.028	0.871
Serum Vitamin D/Platelet count	-0.345	0.039*

*significant at p< 0.05

DISCUSSION

This study is a cross-sectional case control study that assayed the serum vitamin D level among 36 CLL patients and 36 age matched control. Over 86.1% of the CLL patients were over 50years and 66.7% were females. This was similar to observation by Omoti et al[18] in South-south Nigeria which is in contrast to higher male prevalence seen in western literature[8].

The study also revealed that 75% of the patients had high risk disease while 25% had intermediate risk disease and none had low risk disease, this is similar to observation by Omoti et al[18] in which 88.3% of the patients presented with intermediate and high-grade disease while 11.7% had low grade disease. This is a stark contrast to the observation by Tadmor et al where 80% to 90% of newly diagnosed CLL patients had asymptomatic early-stage disease (low-risk disease)[14]. In low risk stages of CLL, the patient may be asymptomatic and the diagnosis may be an incidental finding during routine check-up or for other indications, whereas, most of our patients present following development of symptoms such as progressive lymphadenopathy, organomegalies and cytopaenias, which are usually indicators of a progressive disease. Other reasons may include poor

socio-economic status which prevents patients from seeking care when symptomatic and poor awareness of the disease leading to misdiagnosis of the disease also contributing to delays in the presentation of the patients in earlier stages of the disease.

The mean and standard deviation of serum Vitamin D in the CLL group was 32.08 ± 14.11 ng/ml while that of the control group was 49.06 ± 18.82 which is significantly higher, a finding that is similar to the observation made by Dheghani et al[17] and Kılıçaslan et al[19] in their study. The reason for the low serum Vitamin D may be related to the poor performance status, limiting mobility and sunlight exposure, associated with high risk and intermediate risk disease.

The prevalence of Vitamin D deficiency in CLL patients was 52.8% compared to 5.6% in the control group. This finding is similar to the findings of Tadmor et al which demonstrated that 30% to 50% of CLL patients had suboptimal vitamin D levels[14]. This high prevalence of Vitamin D deficiency could be because majority of the CLL participants are elderly with high-grade disease and poor performance which could translate to reduced mobility and sunlight exposure. Malabsorption of nutrient is common in patients with lymphoid malignancies and could also be responsible for the high prevalence of vitamin D deficiency.

In this study no significant correlation was found between age, lymphocyte count, neutrophil count, haematocrit, and the Rai stage of CLL patients with serum Vitamin D and this is similar to the finding from work done by Dehghani et al in Iran in which 86 CLL patient participated. In their study the mean serum Vitamin D concentration was found to be significantly lower in CLL patients than that of control, they also observed no correlation between sex, age, stage, and Vitamin D3 serum levels[19]. However, in the same study serum Vitamin D was observed to have a negative correlation with spleen size. In a retrospective study carried out by Kılıçaslan et al in Turkey they observed a statistically significant difference in the comparison of the Rai stage-0 group and Rai stage-2 group, Rai stage-0 group and Rai stage-4 group, but no correlation to age and sex of the CLL patients.[17]

In this study the platelet count was found to be negatively related to serum Vitamin D. The reason for this negative correlation is not clear but could be related to high prevalence of high risk disease which is characterised by low platelet count. In a similar study by Talebzadeh et al, platelet count and mean platelet volume (MPV) were found to be significantly higher in the patients with vitamin D deficiency than in the patients without vitamin D deficiency[21,22]. Therefore, our finding suggests that vitamin D deficiency could also be an indicator of worsening disease.

Vitamin D has been studied for centuries, its roles in bone homeostasis, calcium regulation, immunity, cell circle regulation and more recently oncogenesis being investigated. Vitamin D deficiency is a global health problem with over a billion people having either an insufficient or low serum levels. Serum Vitamin D level has a positive relation with rate of disease progression in CLL and as such Vitamin D deficiency is a poor prognostic factor[14]. Low levels of vitamin D are associated with a shorter time to first treatment and inferior overall survival in patients with chronic lymphocytic leukemia (CLL) as demonstrated by Tadmor et al., and Kubeczko et al,[14,15,16]. At present, cytogenetic and molecular markers are used to determine the prognosis and to guide the treatment of CLL. The main ones are TP53 mutation and IGHV gene mutation status[17]. In many parts of the world, especially in low-income countries, there are difficulties in accessing cytogenetic and molecular analyzes due to their high cost. For this reason, low-cost and easily accessible markers may be attractive to some researchers[17]. Therefore, whether vitamin D would provide this much needed alternative remains an open question[14].

CONCLUSION

In conclusion, the study showed a significantly lower mean serum Vitamin D in CLL patients compared to control and a significantly higher prevalence of Vitamin D deficiency in chronic lymphocytic leukemia (CLL) compared to the control. No correlation was demonstrated between vitamin D, age, Rai stage, neutrophil count, lymphocyte count, and hematocrit. However, a negative correlation was observed between platelet

count and Vitamin D.

Recommendations

Serum vitamin D assay should be part of routine investigation done at diagnosis of CLL so that deficiency can be corrected early. Patients with vitamin D deficiency should be followed-up carefully to document the clinical course of their illness compared to those without deficiency. A more comprehensive study involving multiple centers from different zones of country with more participant to compare the relationship between vitamin D and other prognostic factors.

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