ARTICLE / INVESTIGACIÓN

Role of Vitamin D in the diagnosis of acute Myeloid Leukemia

Noor Thair Tahir[1], N. A Thamer[2]*, Noah A .Mahmood[3]
DOI. 10.21931/RB/2023.08.01.50
[1] National Diabetes Center, Mustansiriyah University, Baghdad, Iraq.
[2] Medical Technical College, Al-Farahidi University, Al-Jadiriyah Bridge, Baghdad, Iraq.
[3] Iraqi Center for Cancer and Medical Genetics Research, Mustansiriyah University, Baghdad, Iraq.
Corresponding author: neran.technical@gmail.com

Abstract: A range of hematological and biochemical markers have been investigated in Acute Myeloid Leukemia (AML) patients to determine the relationship between cancer growth and metabolic problems. This study aimed to determine the effects of vitamin D deficiency in Iraqi patients with acute myeloid leukemia who had recently been diagnosed. There was a significant inverse correlation between the total serum cholesterol (TC) level of acute myeloid leukemia (AML) patients group [(148.77±12.2) for males, (165.29±9.64) for females] and the control group [(164.50±7.26) for males, (180.05±7.31) for females], also an inverse correlation between high-density lipoprotein (HDL) level of acute myeloid leukemia (AML) patients group [(46.00±2.04) for males, (46.18±1.08) for females] and control group [(54.25±1.86) for males,(51.94±1.37) for females]. A significant difference was between the serum triglyceride (TG) level of acute myeloid leukemia (AML) patients group [(128.71±13.07) for males, (152.48±10.6) for females] and control group [85.12±11.30) for male, (90.50±10.90) for females], also between vitamin D level of acute myeloid leukemia (AML) patients group [(17.23±1.18) for males, (12.96±0.74) for females] and control group [(42.62±1.43) for males, (40.76±0.82) for females]. A statistically significant difference was between the serum calcium levels of individuals with acute myeloid leukemia [(8.99±0.32) for males, (8.91±0.23) for females] and the control group [(13.13±1.16) for males, (10.73±0.28) for females]. AML patients can benefit from vitamin D treatment, according to a pairwise analysis of receiver operating characteristic (ROC) curves. The above results are related to concluding that Vitamin D can be utilized as a diagnostic test for AML patients.

Key words: Acute myeloid leukemia (AML), Hypereosinophilia, ROC curve, hypocholesterolemia, vitamin D.

Introduction

Leukemia is a type of cancer that affects the blood and blood-forming tissues, such as the bone marrow and the lymphatic system. Several risk factors for leukemia have been identified, including smoking, a genetic disorder such as Down syndrome, exposure to a large amount of radiation or exposure to specific chemical compounds such as benzene, certain chemotherapy used to treat previous cancer, and having a family history of leukemia[1]. Chronic leukemia progresses more slowly than acute leukemia. Patients have a higher proportion of mature cells. In acute leukemia, the immature cells are rapidly advancing, and these cells cannot perform their normal functions[2]. Malignancy myeloid cells lead to myeloid leukemia, whereas that including T and B lymphocytes leads to lymphocytic leukemia[3]. Acute myeloid leukemia (AML) is a cancer that develops when long-lived myeloid blasts in the bone marrow and peripheral blood undergo unchecked transformation and proliferation. Normal cells are replaced by malignant ones, lowering the number of healthy cells[4].

Lipid metabolism disorders are characterized by anomalies of lipids and lipid metabolites occurring mostly in plasma and other tissues, which cause genetic or acquired factors[5]. Several related genes, hormones and enzymes organize the level of lipids. Abnormalities of these factors lead to lipids metabolism disorders, which cause cardiovascular disorders, metabolic diseases and cancers[6]. Different studies have indicated that abnormal levels of lipids are closely related to carcinogenesis and cancer metastasis. Malignant cancer cell proliferation requires high energy to transform and accelerate, leading to lipid metabolism alterations[7]. Some studies showed a decrease in plasma lipid levels in patients with cancer. This may result in increased utilization of blood lipids by malignant cells as a competing factor[8]. Despite these positive correlations between hypercholesterolemia and carcinogenesis, some epidemiologic observations suggest no association exists between cholesterol and cancer progression[9].

Different studies have reported a relationship between Vitamin D deficiency and AML[10]. An inverse relationship exists between circulating vitamin D levels and malignancy for colorectal[11] and breast cancer[12]. This research sought to determine the levels of lipids, high-density lipoprotein (HDL), calcium, vitamin D, and various aspects of the hematological picture in newly diagnosed Acute Myeloid Leukemia (AML) patients in Iraq, with the ultimate goal of improving treatment outcomes.

Materials and methods

This study proceeded at the National Center for Hematology of Al-Mustansiriyah University in Baghdad from April 2019 until November 2019. This research enrolled 55 newly diagnosed AML patients before any specific medication was administered. Their ages ranged from (33-80) years and were compared to 26 healthy people who served as a con-

Citation: Thair Tahir N, Thamer N. A, Mahmood N A. Role of Vitamin D in the diagnosis of acute Myeloid Leukemia. Revis Bionatura 2023;8 (1) 49. http://dx.doi.org/10.21931/RB/2023.08.01.49
Received: 23 December 2022 / **Accepted:** 30 January 2023 / **Published:** 15 March 2023

trol group. Body mass index was determined as weight in kilograms divided by the square of height (kg/m^2). Before starting therapy for AML, blood samples were taken from patients at diagnosis and before they were treated for AML. The separated serum was used for total cholesterol, triglycerides and HDL measurements by Auto Analyzer Kenza 240 TX (Biolabo, France). Vitamin D3 was determined by a mini vidas analyzer (biomerieux, France). Serum Ca was measured by the easy kit analyzer. (Beckman Coulter, Ireland) were used to analyze the Complete Blood Count (CBC).

Statistical Analysis

SAS was used to analyze the data statistically (Statistical Analysis System - version 9.1). To determine if there were any statistically significant differences between means, a one-way ANOVA and the Least Significant Differences (LSD) post hoc test were used. The p-value ($P < 0.05$) is regarded as statistically significant when it is less than one. The receiver operation characteristic (ROC) curve was used to determine the validity of markers as indicators of illness in a particular population. The area under the curve (AUC) of the features was calculated and compared (AUC). The analysis was completed with the help of the Med Calc software[13,14].

Results

This study reported different parameters for patients with AML compared with the control. In table (1), some of the baseline characteristics showed no change in an age when compared between patients and controls; there were increases in the weight of male patients and base mass index. Moreover, some of the hematological studies showed no change in values of Red blood cells (RBC), Basophils but increased Eosinophil values when compared between patients and controls.

Table 2 determined total serum cholesterol, triglyceride, high-density lipoprotein lipids, serum calcium and vitamin D for AML compared with the control. There was a decrease in TC, HDL,D 3 and calcium, while there was an increase in TG.

Figures 1 (A and B) illustrate the receiver operating characteristic curve (ROC) for calcium (A) and vitamin D (B).

Figure hows the area under the curve (AUC) for vitamin D and calcium. While in table 3 shows the AUC, standard error (SE) and confidence interval (CI) for vitamin D and calcium.

Discussion

There was no statistically significant difference in age between the patients and the control group. However, there was a statistically significant difference in male weight between the control and the patients (Table 1) and a significant difference in BMI among males and females. Being overweight was related to raised risk of AML. Adipose tissue is one of the active and complex endocrine organs. Recent studies highlighted the bidirectional interactions, based on adipokines and lipids, between white adipose tissue and tumors and their role in cancer progression (later, "adipose tissue" will refer to white adipose tissue). In addition, adipocyte-secreted factors have been shown to regulate the expression of genes associated with cancer progression (adhesion, invasion, angiogenesis, signal transduction and apoptosis) in non-cancerous mammary cells suggesting a role in cancer initiation[15]; they may also participate to the leukemogenesis of AML[16].

Hypereosinophilia is classified to Primary (Chronic eosinophilic leukemia, Familial eosinophilia, Clonal hypereosinophilia, and Idiopathic hypereosinophilia) and secondary (Infections, autoimmune diseases, allergic diseases, drugs

		Age	Weight	BMI	RBC	BAS	EO
control	Male no=8	36.00±1.19 a	69.62±4.54 b	24.75±1.44 b	5.67±0.49 a	0.02±0.001 a	0.26±0.04 b
	Female no=17	39.05±1.52 a	74.58±2.63 ab	25.86±0.79 b	5.47±0.32 a	0.04±0.02 a	0.28±0.04 b
patients	Male no=26	42.15±2.82 a	81.15±2.25 a	29.05±0.95 a	5.67±0.49 a	0.03±0.01 a	0.49±0.06 a
	Female no=27	42.55±2.81 a	74.92±2.32 ab	27.00±0.64 ab	5.21±0.24 a	0.06±0.02 a	0.41±0.04 a
	LSD	8.9252	8.396	2.8467	0.8996	0.0657	0.1385

Small letters within a single column represent the comparison between the control and patients. Different letters mean significant results.

Table 1. Baseline characteristics and some hematological parameters in AML patients and controls.

		TC	TG	HDL	D3	Ca
control	Male no=8	164.50±7.26 a	85.12±11.30 b	54.25±1.86 a	42.62±1.43 a	13.13±1.16 a
	Female no=17	180.05±7.31 a	90.50±10.90 b	51.94±1.37 a	40.76±0.82 a	10.73±0.28 b
patients	Male no=26	148.77±12.2 b	128.71±13.07 a	46.00±2.04 b	17.23±1.18 b	8.99±0.32 c
	Female no=27	165.29±9.64 b	152.48±10.6 a	46.18±1.08 b	12.96±0.74 b	8.91±0.23 c
	LSD	5.17	5.68	5.4416	3.3389	1.1895

D3= vitamin D, TC =total cholesterol, TG = triglyceride, HDL= high-density lipoprotein. Small letters within a single column represent the comparison between the control and patients. Different letters mean significant results.

Table 2. Some biochemical studies for AML and control.

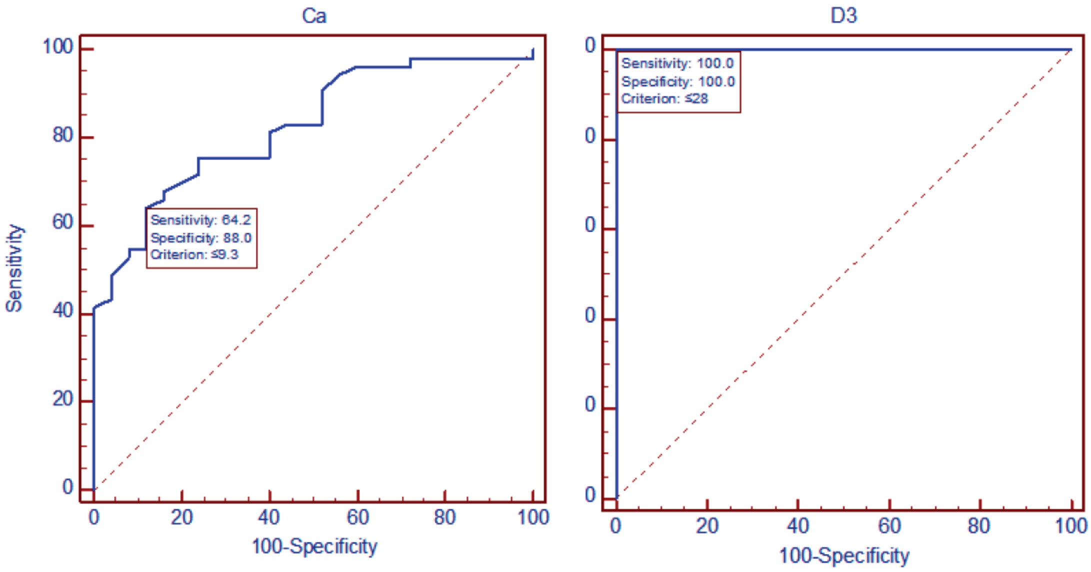

Figure 1. ROC curve for identifying optimal calcium (left) and vitamin D (right) cutoff points.

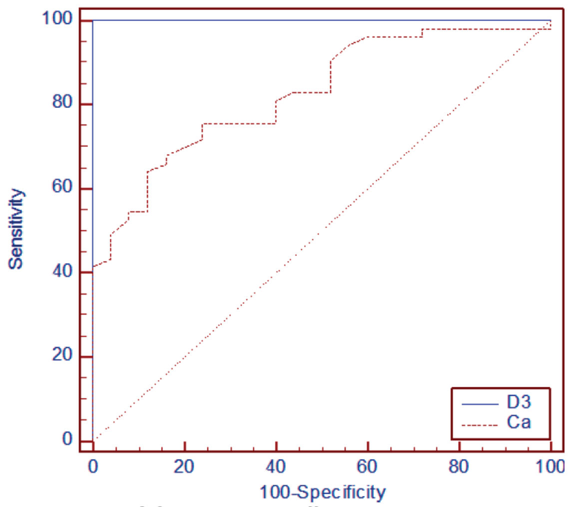

Figure 2. The ROC curves with different areas under the curve.

Variable	AUC	SE [a]	95% CI [b]
D3	1.000	0.000	0.954 to 1.000
Ca	0.826	0.0465	0.724 to 0.903
Pairwise comparison of ROC curves			
D3 ~ Ca Significance level	P = 0.0002		

Table 3. AUC, SE and CI for vitamin D and calcium.

and Malignancies)[17]. Through search in articles, we found similar results were matched with our results[18,19]. Many surveys have been performed considering the serum lipids abnormalities[20]; in table 2, no statistically significant variations in plasma total cholesterol, triglycerides, or high-density lipoprotein were detected between men and females, neither for AML patients nor controls. There was a considerable decrease($p<0.05$) in cholesterol and HDL, whereas triglycerides value a significantly elevated($P<0.05$) when compared with males between(patients and controls) and females between (patients and power). This results in agreement with the other findings[21]. Different researchers explained the relation between hypocholesterolemia and the stage of maturation of leukemic blast cells in acute myeloid leukemia[22]. The elevated LDL receptor in AML patients was caused by hypocholesterolemia[23]. Several research has been conducted to characterize HDL's potential to boost proliferation, immigration, and survival in cancer cell cultures[24]. According to many studies, HDL-C is related to an increased risk of cancer because it continues to provide extra cholesterol to and fuel the development of the tumor[25].

In this study, we found a low level of Vitamin D in newly diagnosed AML patients before the beginning of their treatment. In the Middle East, different factors cause Vitamin D deficiency, such as Low exposure to sunlight, lack of Vitamin D in food, the nature of clothes, type of skin, and lack of complements[26]. But, recently, the use of Vitamin D supplements has obtained great interest among older adults; they essentially have sufficient levels of Vitamin D[27]. Different epidemiological and experimental studies support that Vitamin D deficiency has increased the risk of developing several cancers[28]. Various studies have indicated that Vitamin D can usually modify several critical cellular methods, involving suppression of carcinogenesis by creating cellular differentiation, suppression of proliferation and promoting apoptosis[29,30]. Vitamin D has other significant effects, such as inhibiting tumor angiogenesis, invasion and metastasis[31].

On the other hand, a previous study showed a positive correlation between low vitamin D levels and higher BMI or obesity[32]. Hypocalcemia is unusual in hematoma malignancy. Various factors, including low albumin, inadequate nutrition, low vitamin D, low magnesium, or persistent respiratory alkalosis, may cause it. In tumor lysis, increased serum phosphorous may cause calcium-phosphate deposition, decreasing serum calcium[33]. Figures 1 (A and B) illustrate the receiver operating characteristic (ROC) curves. Generally, the ROC curve measures a test's effectiveness by establishing appropriate cutoff points. The graph depicts calcium sensitivity, and specificity (A) was 64.2. % and 88.0%, then sensitivity and specificity for vitamin D (B) were 100.0% and 100.0%, respectively.

Table 3 shows that AUC for vitamin D was 1.000 (95% CI = 0.954–1.000), and AUC for calcium was 0.826 (95% CI = 0.724 –0.903). The AUC is a standard measure of the accuracy of a diagnostic test. Tests are often classed based on the area under the ROC curve (figure 2). The bigger the AUC, the higher the test's total score. The positive and false favorable rates for the vitamin D test (figure 1) are greater than those for calcium test A at all cutoffs, making it the better choice. The AUC for vitamin D is larger than the area under the curve for the calcium test. The pairwise comparison of the ROC curves revealed a statistically significant difference (P= 0.0002) for vitamin D and calcium parameters. In a paired ROC analysis, the vitamin D measure was shown to be more discriminatory than the calcium measure. A perfect test has an AUC of 1.0. So that vitamin D is an ideal test for diagnostic AML patients than calcium. Recently, cancer disease can be diagnosed by PCR, such as CML[34] and Adenocarcinoma[35,36]. This molecular technique was also employed to diagnosis different microorganisms that caused pathogenicity in human such as *Clostridium perfringens*[37], *Brucella melitensis*[38], *Proteus vulgaris*[39,40], *Staphylococcus aureus*[41], *Pseudomonas aeruginosa*[42,43] , and *Toxoplasma spp*[44,45].

Conclusions

The pairwise comparison among the ROC curves for vitamin D and calcium showed that the vitamin D measure was more discriminative than calcium. So vitamin D is a perfect test for early diagnosis of AML patients.

Acknowledgments

Thanks going to all who support us.

Funding

Self by authors.

Conflicts of Interest

No conflict.

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