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Original Research Article

Study the effect of Vitamin D3 in newly diagnosed acute myeloid leukemia

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ABSTRACT

Objective: This study is aimed to put light on the effect of vitamin D3 (VitD3) in newly diagnosed acute myeloid leukemia (AML) patients.
Materials and Methods: The AML patients consisted of sixty patients (30 male, 30 female). The average age of patients was (36.44±8.44) years (range 25-45). Thirty healthy subjects were considered as controls (15 male and 15 female), and the average age of control group was (32.22±5.13) years. All subjects had to go through clinical examination to determine existence of other diseases in addition to evaluate some tests as complete blood count [hemoglobin (Hb), platelet (PLT), and white blood cells (WBCs)], ferritin, FBS (fasting blood sugar), TG (triglycerides), TC (total cholesterol), and HDL (high density lipoprotein cholesterol) (HDL-Ch), urea, and creatinine. Vitamin D3 was measured by minividase Biomerux/French.
Results: The VitD3 was highly significantly lower in AML patients than in controls (p=0.001). While, VitD3 was lower in male than in female AML patients but the difference was not statistically significant. There were statistically significant positive correlations between VitD3 and Hb, PLT, Wbc, ferritin, FBS, and TG in both male and female AML patients.
Conclusion: These findings suggest that lower serum concentrations of vitamin D3 may possibly be considered as a potential factor for early assessment of acute myeloid leukemia.

1. Introduction

Acute myeloid leukemia (AML) which is defined as a hematological malignancy characterized by the proliferation of progranulocytes or myeloblasts that failed to developed normal myeloid differentiation.[1] It comprises a heterogeneous group of clinically and biologically aggressive disorders which driven by any combination or number of chromosomal abnormalities, recurrent gene mutations, and/or altered signaling pathways.[2] Based on the French-American-British leukemia experts, Acute myeloid leukemia are morphologically classified into 8 subtypes(M0 to M7). Markedly, over 700 chromosomal abnormalities was detected in leukemic cells of the AML patients.[3] In 2018, the global incidence of AML has been estimated to be nearly 130,000.[4] AML tends to mainly affect older adults, with a median age of onset of sixty-eight years.[5]

Vitamin D (VitD), is a fat-soluble vitamin that is obtained from sun exposure, food, and supplements.[6] VitD is a steroid hormone which produced by human skin as a result of ultraviolet (UV) radiation stimulus.[7] VitD is important for calcium as well as bone metabolism. In addition, it has other roles that includes: reducing insulin resistance , ameliorating oxidative stress, and reducing the possibility

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of prevalent metabolic syndrome.[8]

1,25-Dihydroxy-vitamin D3, a vitamin D (cholecalciferol) active metabolite (1,25D3, calcitriol), is a secosteroid hormone with a variety of biological functions.[9] regulating the uptake and distribution of necessary minerals, such as calcium, magnesium, and phosphorus, which are essential for maintaining bone health, is one of 1,25D3's key physiological roles.[10] VitD3 regulates gene transcription through binding to vitamin D receptor (VDR). VitD3, which is not dependent on transcription, can also elicit rapid intracellular responses in vitro.[11]

VitD was implicated in the pathogenesis of hematologic malignancies and showed promise as an anticancer drug. Serum 25(OH) D3 concentrations, the precursor of calcitriol, are usually lower in subjects with hematological disorder in comparison with healthy subjects. A worse illness outcome is commonly linked to this. Moreover, cancer models both in vitro and in vivo have shown that sick cells frequently produce high levels of the VDR, which is required for many of the anticancer effects.Importantly, "in abnormal hematological cells, vitamin D supplementation promotes apoptosis, induces differentiation, inhibits proliferation, sensitizes tumor cells to other anti-cancer therapies, and reduces the production of pro- inflammatory cytokines".[12]

This study is aimed to put light on the effect of VitD3 in patients with newly diagnosed AML.

2. Subjects and Methods

Acute myeloid leukemia patients consisted of sixty patients (30 male, 30 female). The patients' average age was (36.44±8.44) years (range 25-45). Thirty healthy subjects were considered as controls (15 male and 15 female), while the control group's average age was (32.22±5.13) years. This investigation was done at the National Center of Hematology during the period from 1st December 2020 till 30th June 2021. All subjects had to go through clinical examination to determine existence of other diseases in addition to evaluate some tests as complete blood count [hemoglobin (Hb),platelet(PLT), and wite blood cells (WBCs)], ferritin, urea, creatinine, Fasting blood sugar, total cholesterol, triglycerides, and high density lipoprotein (HDL) (FBS). Minividase Biomerux/French was used to calculate vitamin D3 levels.

In accordance with the Helsinki Ethical Guidelines, this investigation was completed. Using SPSS, a statistical analysis was performed. The investigation's findings are expressed as mean ± standard deviation. Using the student's t-test, the mean values of the two groups were compared.The P-value 0.05 or lower was regarded as significant.

3. Results

The hematological and biochemical parameters of the AML patients and controls are summarized in Table 1. FBS, TC, TG, and urea were all statistically significantly higher in newly diagnosed AML patients compared to controls (all p=0.05), and WBC (p=0.01). In comparison to controls, PLT and ferritin levels in AML patients were highly significantly lower. Compared to the controls, VitD3 levels in AML patients were significantly lower (p 0.001). Hb and HDL-Ch were statistically significantly decrease (p=0.05 and p=0.016, respectively) in AML patients compared to controls. However, regarding creatinine levels, there were no statistically significant changes between AML patients and controls.

The AML patients are broken down by sex in Table 2. Male versus female AML patients had statistically significantly higher levels of Hb, PLT, TC, TG, and ferritin. Although the difference was not statistically significant, male AML patients had lower VitD3 levels than female AML patients.The WBC was statistically significantly lower in male compared with female AML patients (P=0.01). Nevertheless, There were no statistically significant differences found in FBS, HDL-Ch, urea, and creatinine between male and female AML patients.

Table 3 showed that there were statistically significant positive correlations between VitD3 and Hb (r=0.333, r-0.244), PLT (r=0.330, r=0.296), Wbc (r=0.305, r=0.284), ferritin (r=0.338, r=0.374), FBS (r=0.325, r=0.203), and TG (r=0.662, r=0.665) in male and female AML patients respectively.

4. Discussion

In this investigation, highly significantly lower VitD3 level was found in AML subjects compared to the control group. Similar to earlier investigations.[13–16] One of these investigations was performed by Bobilev et al.[14] who detected low levels of 1.25 (OH)D in human acute myeloid leukemia cell lines.

In addition, Elkerdany et al.[13] and Zidan et al.[15] established that VitD contribute to the regulation of cellular proliferation, differentiation accompanied by angiogenesis and apoptosis. Furthermore, Munker and his team[17] revealed that VitD is a highly potent inhibitor of the CD34 leukemic cells, whereas maintaining activity of the normal CD34 hematopoietic stem-progenitor cells. Lappe et al. and these findings are usually in agreement.[18] They demonstrated that a major independent predictor of the risk of cancer was the serum 25(OH)D level., in addition to vitamin D and supplemented calcium being associated with a lower risk of cancer.. Additionally, Thomas and his coworkers[19] revealed a significant relationship between malignant cell burden and circulatory 25(OH)D. They reported that the lower concentrations of

Table 1: The hematological and biochemical parameters of the aml patients and controls

Parameters	AML N (60) Mean±SD	Control N (30) Mean±SD	P-value
Hb (g/dl)	10.6±1.66	13.7±1.12	0.05*
PLT(103/μl)	98.5±7.7	206.2±18.1	0.001**
WBCs (103/μl)	25.5±1.55	8.44±1.23	0.01**
Ferrtin (ng/ml)	35.4±5.56	85.1±15.5	0.01**
FBS (mg/dl)	97.4±12.5	79.9±13.32	0.05*
TC (mg/dl)	220.11±22.41	168.1±18.02	0.05*
TG (mg/dl)	168.33±13.4	120.5±11.4	0.05*
HDL-Ch (mg/dl)	44.5±4.01	46.1±5.8	0.016*
Urea (mg/dl)	45.4±6.06	25.3±5.2	0.05*
Creatinine (mg/dl)	0.83±0.31	0.65±0.11	0.220
Vitamin D3 (ng/ml)	12.4±6.81	38.6±4.2	0.001**

Levels of significance= *P<0.05, and **P<0.01.
Hb: hemoglobin, PLT: platelet, WBCs: white blood cells, FBS: fasting blood sugar, TC: total cholesterol, TG: triglyceride, HDL-Ch: high density lipoprotein cholesterol.

Table 2: The hematological and biochemical parameters betweenmale and female aml patients

Parameters	Male N (30) Mean±SD	Female N (30) Mean±SD	P-value
Hb (g/dl)	12.0±1.50	9.32±0.88	0.05*
PLT (103/μl)	69.5±5.71	35.10±5.11	0.05*
WBCs (103/μl)	10.8±1.66	16.6±0.74	0.01**
Ferritin (ng/ml)	30.7±10.0	15.2±8.12	0.01**
FBS (mg/dl)	87.3±8.77	94.2±8.4	0.130
TC (mg/dl)	224±15.41	198.4±31.22	0.05*
TG (mg/dl)	187.5±11.0	170.44±10.14	0.05*
HDL-Ch (mg/dl)	44.9±10.4	46.2±5.21	0.132
Urea (mg/dl)	25.4±1.7	26.3±1.8	0.142
Creatinine (mg/dl)	0.73 ±0.32	0.72±0.43	0.175
Vitamin D3 (ng/ml)	16.86±3.40	28.9±3.01	0.51

Levels of significance= *P<0.05, and **P<0.01.
Hb: hemoglobin, PLT: platelet, WBCs: white blood cells, FBS: fasting blood sugar, TC: total cholesterol, TG: triglyceride, HDL-Ch: high density lipoprotein cholesterol.

Table 3: Correlation coefficient between VitD3 levels and allparameters in both genders (male and female) AML patients.

Parameters	Vitamin D3 Male r	Female r
Hb (g/dl)	0.333*	0.244*
PLT (103/μl)	0.330*	0.296*
WBCs (103/μl)	0.305*	0.284*
Ferritin (ng/ml)	0.338*	0.374*
FBS (mg/dl)	0.325*	0.203*
TC (mg/dl)	0.139	0.026
TG (mg/dl)	0.662**	0.665**
HDL-Ch (mg/dl)	0.149	0.113
Urea (mg/dl)	0.131	0.102
Creatinine (mg/dl)	0.102	0.032

Levels of significance= *P<0.05, and **P<0.01.

circulatory 25(OH)D seemed to be associated with disease aggressiveness, the progressive phase of the disease along with poor response to treatment. Hence, it is a potential biomarker of prognosis in subjects with acute myeloid leukemia.

In this investigation, no statistically differences in VitD3 levels were found between male and female AML patients. Epidemiologic studies implied a relationship between AML and low 25(OH) vitamin D3 concentrations. For instance, a research in United Arab Emirates[20] reported female predominance in AML, even though the population of United Arab Emirates consists of more males than females, and even though it is very widely known that acute myeloid leukemia is more common in males. These results indicate that the low VitD3 concentrations secondary to the practice of females wearing conservative clothing can possibly contribute to higher incidence of acute myeloid leukemia.[20]

In this study, VitD3 levels showed significant positive correlations with Hb, PLT and WBC in both male and female AML groups. Elkerdany et al.[13] reported a positive correlation between VitD and PLT, while no correlations between VitD with Hb and WBC were found in AML subjects.

Globally, numerous investigations were performed to examine the relationship between ferritin and VitD. Serum ferritin concentrations are regulated by hepcidin, that plays a central role in decreasing human intestinal iron absorption. VitD "regulates the hepcidin-ferroportin axis in macrophages", in addition, the increase of VitD is known to lower systemic concentrations of hepcidin which ameliorate anemia.[21] In this investigation, VitD3 and serum ferritin levels showed a positive correlation. This result agreed with other investigations, where a positive association was seen in adults,[22] children and adolescents,[23] and fibroid uterus.[24]

It has been reported in different investigations that VitD has an important role in control of circulating glucose concentrations and its utilization in target tissues. Numerous human and animal investigations have demonstrated the role of VitD in insulin synthesis in addition to its secretion from the beta cells.[25] It has shown that there was a significant positive correlation between VitD3 and FBS in male and female AML patients in the current study. Nonetheless, this result contradicts those of other previous studies in different populations.[26,27] Many lines of strong evidence suggest that vitamin D3 affects insulin resistance, systemic inflammation, and impaired pancreatic beta cell activity.[28] VitD3 can alter insulin sensitivity to raise blood glucose levels because it has been found that numerous tissues, including pancreatic islet beta cells, contain VitD3 receptors.[26]

Due to the lack of sufficient sun exposure, a main cause of VitD deficiency, is considered to be linked to elevated serum cholesterol concentrations,[29] it seems plausible that VitD deficiency plays an essential role in hypercholesterolemia. Moreover, the association between cholesterol and VitD status might be evaluated since both serum cholesterol (involving TC, HDL-Ch, and LDL-Ch) and 25(OH)D3 concentrations are routinely assessed from the blood samples that taken in research investigations. A literature search showed a common trend in which low 25(OH)D3 concentrations were linked to increased LDL-Ch and TC concentrations, increased LDL-Ch/HDL-Ch ratio and TC/HDL-Ch ratio, or reduced HDL- Ch concentrations. These trends have held true in diverse patient populations which included individuals of different ages and ethnicities. Consequently, there is significant evidence to support the idea that VitD deficiency plays an essential role in hypercholesterolemia. Nevertheless, these "cross-sectional" studies might only offer relationships and not causality.[30] The presence of cholesterol in the blood and tissues has been consistently demonstrated to have a major role in the pathogenesis of ischemic heart disease, but the relationship of cholesterol to cancer, such as breast, leukemia, and colorectal cancer, has also been revealed.In cell membranes, the cholesterol content is tightly regulated, furthermore, this process of regulation includes the uptake of LDL-Ch. Nonetheless, intriguingly, cholesterol accumulation was detected in various types of solid tumours, particularly prostate and oral cancers. Moreover, dysregulated cholesterol metabolism represents a significant metabolic alteration in several malignancies, involving breast and lung cancers as well as myeloid leukemia.[31] Males with hypertriglyceridemia may benefit from lowered serum TG concentration as well as extensive colonoscopic surveillance in colorectal cancer, even if a high serum TG concentration does not appear to be mechanically implicated in the formation of most malignancies.[32] A relationship between colorectal cancer and high serum TG was as well detected.[33] In this investigation, VitD3 and TG showed a statistically significant positive correlation in both male and female AML patients.

5. Conclusion

the result of this investigation revealed that lower serum concentrations of vitamin D3 may possibly be considered as a potential factor for assessment of acute myeloid leukemia.

6. Conflict of Interest

None.

7. Source of Funding

None.

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