AIMS Medical Science

AIMS Medical Science, 11(1): 47–57.
DOI: 10.3934/medsci.2024004
Received: 26 December 2023
Revised: 23 February 2024
Accepted: 04 March 2024
Published: 13 March 2024

http://www.aimspress.com/journal/medicalScience

Research article

The relationship of vitamin D levels with hemogram indices and metabolic parameters in patients with type 2 diabetes mellitus

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Abstract: Background: Vitamin D deficiency and Type 2 Diabetes (T2DM) are two important health problems that have rapidly increased prevalences in recent years. Chronic inflammation and susceptibility to infection are the characteristic features of T2DM. Vitamin D deficiency has been associated with high serum inflammatory marker levels due to its immunomodulatory effect. Moreover, studies have pointed out that vitamin D insufficiency could be associated with T2DM. Additionally, in recent years, inflammatory markers derived from hemogram have been associated with diabetes and its complications. Therefore, in our study, vitamin D levels, metabolic markers (i.e., serum uric acid, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol), and hemogram indices were analyzed in well controlled and poorly controlled T2DM patients. Furthermore, we compared those variables in vitamin D deficient and non-deficient groups. Methods: Laboratory data, including vitamin D and hemogram markers, were compared between poorly and well controlled T2DM patients who visited the outpatient internal medicine clinics of our institution. **Results:** A total of 240 T2DM individuals were included in the present study: 170 individuals had vitamin D deficiency and 70 individuals had normal vitamin D levels, who served as controls. The median neutrophil to lymphocyte ratio (NLR) value was 2.2 (0.74–7.4) in the vitamin D deficient group and 2.02 (0.73–5.56) in the vitamin D normal group ($p = 0.025$). Among the study parameters, the NLR and glycated hemoglobin (HbA1c) levels showed a significant positive correlation ($r = 0.30$, $p < 0.001$). The sensitivity and specificity of the NLR to predict vitamin D deficiency were determined as 60% and 49%, respectively (AUC: 0.59, $p = 0.03$, 95% CI: 0.51–0.67). The sensitivity and specificity of the NLR to predict an improved control of diabetes were 72% and 45%, respectively (AUC: 0.67, $p < 0.001$, 95% CI: 0.60–0.74). **Conclusions:** We think that NLR can be helpful in follow up of T2DM and vitamin D deficiency.

Keywords: type 2 diabetes mellitus; inflammation; inflammatory marker; vitamin D; neutrophil/lymphocyte ratio

1. Introduction

One of the most common chronic diseases in elderly population is Type 2 Diabetes Mellitus (T2DM) and is considered at the top of the endocrine and metabolic diseases [1]. Worldwide, the prevalence of diabetes mellitus is increasing at a very high rate. T2DM is a chronic metabolic disorder in which individuals cannot sufficiently benefit from carbohydrates, fats, and proteins, this leading to hyperglycemia. It is characterized by progressive insulin secretion defects resulting from the inadequate functioning of pancreatic beta cells [2]. It is known that many environmental and genetic factors play a role in the development of diabetes, such as a history of diabetes in first-degree relatives, obesity, a sedentary lifestyle, and emotional stress. The diagnosis of T2DM is made by evaluating laboratory and clinical findings in conjunction with the patient's complaints.

There are four criteria for diagnosing diabetes, with none being superior to the others: blood glucose (fasting) (at least 8 hours of fasting) ≥126 mg/dl, plasma glucose at the 2nd hour of a 75 g oral glucose tolerance test ≥200 mg/dL, randomly measured blood glucose levels ≥200 mg/dl + clinical signs of diabetes, and an glycated hemoglobin (HbA1c) level ≥ 6.5% (≥48 mmol/mol) [3]. The most common symptoms of diabetes mellitus include frequent urination, excessive thirst, increased appetite, weakness, fatigue, dry mouth, and nocturia (waking up to urinate at night). Less common symptoms are blurred vision, unexplained weight loss, persistent and recurrent infections, and itching [4].

Chronic inflammation and susceptibility to infection are characteristic features of T2DM. Vitamin D deficiency and the prevalence of T2DM are two health problems that have rapidly increased in recent years. Many studies have found an association between vitamin D deficiency and T2DM [5,6]. Vitamin D deficiency has been associated with high serum inflammatory marker levels due to its immunomodulatory effects. In the context of vitamin D deficiency, elevated serum inflammatory markers have been a significant concern in the literature. Some inflammatory markers derived from a complete blood count, such as the neutrophil-lymphocyte ratio (NLR), the platelet-lymphocyte ratio (PLR), and the monocyte-lymphocyte ratio (MLR), have recently garnered much attention. Additionally, it has been reported that these parameters are related to inflammation [7].

Given the close relationship between hemogram parameters and vitamin D levels with T2DM, this study examines the effects of vitamin D levels in T2DM patients on metabolic markers such as the NLR, the PLR, the MLR, uric acid, high-density lipoprotein (HDL), and low-density lipoprotein (LDL).

In this present study, we aim to evaluate metabolic and hemogram-derived inflammatory markers in well-controlled and poorly controlled T2DM patients. Furthermore, we aim to compare these markers in patients with normal vitamin D levels and subjects with low vitamin D levels.

2. Material and methods

2.1. Patient inclusion

Patients with T2DM who applied to the internal medicine outpatient clinics of Bolu Abant İzzet Baysal University Faculty of Medicine Hospital between February 2022 and July 2022 were included

in our study if they were over the age of 18 years. Patients who were pregnant, or who had end stage kidney disease, cirrhosis, and active infection, and cancer were excluded. Ethical approval was obtained from the Abant Izzet Baysal University ethics committee (approval date: 8th of March, 2022; approval number: 2022/53). We recorded the sociodemographic characteristics, anthropometric, and laboratory data of the patients. Based on their vitamin D levels, 25(OH) vitamin D levels were divided into two groups: below and above 20 ng/ml. Furthermore, the patient population was divided into two groups, according to the HbAlc level: well (HbA1c < 7%) and poor (HbA1c ≥ 7%) diabetic control groups. We compared the general characteristics and laboratory data of the patient groups. A total of 240 T2DM individuals were included in the present study: 170 individuals had a vitamin D deficiency and 70 people had normal vitamin D levels, who served as controls.

2.2. Statistical analysis

The SPSS statistical software (SPSS 16.0, IBM Co., Chicago, IL, USA) was used to analyze the data. The Kolmogorov-Smirnov test was used in a normality analysis of the study variables. Since none of the variables were complied with a normal distribution, we presented them as median (minimum-maximum) values, and the Mann-Whitney U test was used to compare between the groups. The Chi-square test was used to compare categorical variations between groups, and we expressed these parameters as numbers (n) and percentages (%). We used the Pearson correlation analysis test to evaluate the correlation of variables with each other. To examine the sensitivity and specificity of the variables of the study, which further indicates vitamin D deficiency and diabetes regulation, we performed ROC analysis tests. We set a significance level of $p < 0.05$ for statistical significance.

3. Results

When the two groups were evaluated in terms of vitamin D levels, the median value was found to be 12.7 (2.2–19.7) ng/mL in T2DM patients with low vitamin D levels, and the median value was 28 (20–69.7) ng/mL in the normal vitamin D group. There was a significant difference between the two groups ($p < 0.001$).

When the groups in our study were evaluated in terms of biochemical parameters, the HbA1c median value was 8.2 (5–18) in T2DM patients with a vitamin D deficiency, while the HbA1c median value was 7.1 (4.7–10.8) in the group with normal vitamin D values. The HbA1c was significantly different between study groups ($p = 0.005$). The median triglyceride (TG) value was 163 (46–484) mg/dL in the vitamin D deficiency group, while the TG median value was 129 (31–442) mg/dL in normal vitamin D group ($p = 0.006$).

The median Hemoglobin (HGB) value was measured as 13.3 (7.3–16.7) g/dL in the group with vitamin D deficiency and 13.9 (8.5–15.2) g/dL in the group with normal vitamin D levels ($p = 0.006$). The median NLR value was 2.2 (0.74–7.4) in the vitamin D deficient group and 2.02 (0.73–5.56) in the vitamin D normal group ($p = 0.025$). No significant differences were detected between the two groups in terms of the anthropometric measurements and the urea, creatinine, sodium, glomerular filtration rate (GFR), potassium, uric acid, albumin, AST, ALT, LDL, HDL, total cholesterol, and C-reactive protein (CRP) levels, except for the Hb levels from the hemogram parameters and the NLR levels from the hemogram-derived parameters (All parameters are shown in Table 1, Table 2 and Table 3).

Table 1. Comparison of anthropometric measures among low and normal vitamin D groups.

		Median (Min-Max)			
		Low Vitamin D Group	Normal Vitamin D Group	Z	P
Age (years)		57 (24–85)	59 (43–82)	−1.1	0.29
		X^2		X^2	
Gender	Women (n,%)	113 (66.5%)	38 (55.1%)	7.48	0.01
	Men (n,%)	57 (33.5%)	31 (44.9%)		

Table 2. Comparison of serum biochemistry in Low and Normal Vitamin D Groups.

	Median (Min-Max)			
	Low Vitamin D Group	Normal Vitamin D Group	Z	P
HbA1c %	8.2 (5–18)	7.1 (4.7–10.8)	−2.78	0.005
Vitamin D (ng/mL)	12.7 (2.2–19.7)	28 (20–69.7)	−12.2	<0.001
CRP (mg/L)	3.4 (0.1–30.2)	3.5 (0.1–34.5)	−0.95	0.34
FPG (mg/dL)	160 (70–373)	160 (64–418)	−1.43	0.15
Uric Acid (mg/dL)	5.6 (2.4–13.5)	5.6 (3–12)	−1.21	0.64
AST (IU/L)	19 (10–140)	19 (9–89)	−0.56	0.57
ALT (IU/L)	22 (7–103)	22 (8–56)	−0.16	0.87
Urea (mg/dL)	37 (10–221)	37 (15–100)	−1.21	0.22
Creatinine (mg/dL)	0.89 (0.54–5.8)	0.96 (0.51–2)	−1.26	0.21
GFR (ml/min)	85 (7–124)	78.5 (33–112)	−0.85	0.21
Total Chol. (mg/dL)	191 (81–373)	191 (93–289)	−0.01	0.99
TG (mg/dL)	163 (46–484)	129 (31–442)	−2.7	0.006
HDL (mg/dL)	48 (21–378)	48 (32–485)	−0.74	0.46
LDL (mg/dL)	109 (42–345)	109 (31–197)	−0.99	0.32

Table 3. Comparison of hemogram parameters in Low and Normal Vitamin D Groups.

	Median (Min-Max)			
	Low Vitamin D Group	Normal Vitamin D Group	Z	P
WBC (K/uL)	7.6 (3.8–16.5)	7.4 (3.3–16.3)	−0.85	0.39
HGB (g/dL)	13.3 (7.3–16.7)	13.9 (8.5–15.2)	−2.8	0.006
HTC (%)	39.5 (30–49)	41.4 (32–52)	−2.4	0.015
PLT (K/uL)	267 (53–533)	254 (20–438)	−1.2	0.22
MONO (K/uL)	0.6 (0.20–6.5)	0.62 (0.27–1.27)	−0.56	0.57
LYM (K/uL)	2.13 (0.52–7.5)	2.11 (0.87–3.79)	−0.16	0.087
NEU (K/uL)	4.53 (2.15–11.8)	4.2 (1.2–12.32)	−1.4	0.15
NLR (%)	2.2 (0.74–7.4)	2.02 (0.73–5.56)	−2.24	0.025
PLR (%)	121 (22.5–351)	119.9 (18.1–370)	−0.73	0.46
MLR (%)	0.29 (0.10–5.4)	0.29 (0.11–1.03)	−0.52	0.60

Among the study parameters, the NLR and HbA1c levels showed a significant positive correlation ($r = 0.30$, $p < 0.001$). There was a significant negative correlation between the vitamin D

level and the HbA1c level (r = −0.20, p = 0.02). Additionally, there was a significant negative correlation between vitamin D and the serum TG value (r = −0.13, p = 0.04). There was a significant and positive correlation between Fasting blood glucose (FBG) and TG in the study population (r = 0.22, p < 0.001). Table 4 shows the correlation between the study variables.

Table 4. Correlation between study variables.

	NLR	HbA1c	Vitamin D	TG
NLR	-	r = 0.30 p < 0.001	r = −0.1 p = 0.01	NS
HbA1c	r = 0.30 p < 0.001	-	r = −0.20 p = 0.02	NS
Vitamin D	r = −0.1 p = 0.01	r = −0.20 p = 0.02	-	r = −0.13 p = 0.04
TG	NS	NS	r = −0.13 p = 0.04	-

Note: NS—Not Significant.

The sensitivity of the HbA1c levels (>7.15%) to predict vitamin D deficiency was 69%, and the specificity was 50% (AUC: 0.6, p = 0.006, 95% CI: 0.54–0.69). The sensitivity and specificity of the NLR levels (when it is higher than 2%) to predict vitamin D deficiency were determined as 66% and 49%, respectively (AUC: 0.59, p = 0.03, 95% CI: 0.51–0.67) (Figure 1). The NLR levels had a 72% sensitivity and 45% specificity (when it is higher than 1.84%) to predict well diabetes regulation (AUC: 0.67, p < 0.001, 95% CI: 0.60–0.74) (Figure 2). Serum vitamin D (<17.9 ng/mL) has a sensitivity of 47% and a specificity of 71% to predict an improved diabetes control (area under the curve (AUC): 0.55, p = 0.02, 95% CI: 0.47–0.63).

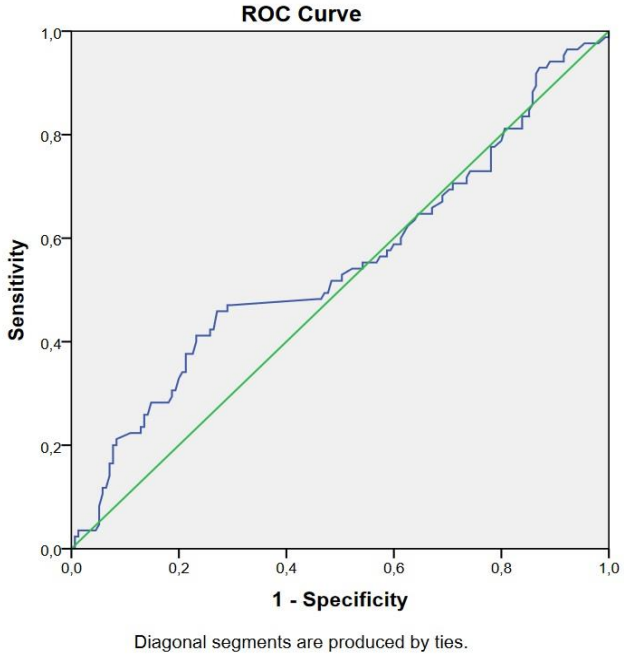

Figure 1. The ROC curve of NLR in determination of Vitamin D Deficiency. The sensitivity and specificity of the NLR level (at >2% cut off value) to predict vitamin D

deficiency were determined as 66% and 49%, respectively (AUC: 0.59, p = 0.03, 95% CI: 0.51–0.67).

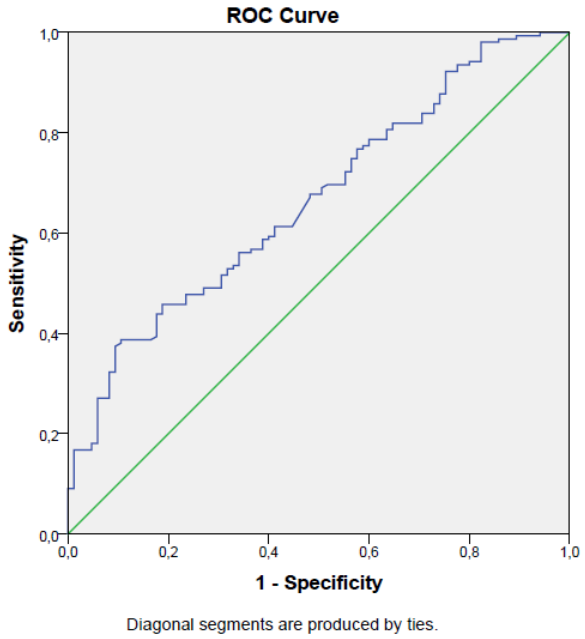

Figure 2. The ROC curve of NLR in Determination of Poor Diabetic Control. The sensitivity and specificity of the NLR level (at >1.84% cut off value) to predict well diabetic control were 72% and 45%, respectively (AUC: 0.67, p < 0.001, 95% CI: 0.60–0.74).

4. Discussions

The most important results of our study can be summarized as follows:

1. Individuals with poorly controlled diabetes were found to have lower vitamin D levels than those with well-controlled diabetes;
2. According to the data we obtained, a large portion of our study population, which consisted of individuals diagnosed with T2DM, had either insufficient or deficient serum vitamin D levels;
3. The HbA1c value in individuals diagnosed with T2DM in the low vitamin D group was higher compared to the normal vitamin D group;
4. The TG value from serum lipids was higher in the group with low vitamin D levels than in those with normal vitamin D levels; and
5. The Hb value, which was one of the hemogram parameters, was lower in the low vitamin D group, and the NLR levels derived from whole blood was found to be higher in low vitamin D group compared to the normal vitamin D group.

Vitamin D deficiency and T2DM, which are known as the pandemic of the age, are common conditions [7,8]. Diabetes is one of the leading health problems with a rapidly increasing incidence in recent years, causing serious complications [9]. In light of numerous recent studies on vitamin D, it has been observed that vitamin D has various functions in the human body, including the expression of the vitamin D receptor in many non-skeletal cells, such as pancreatic beta cells; moreover, it has a role in bone metabolism [10]. There are studies indicating that serum vitamin D levels may contribute to the development of systemic diseases such as T2DM [11,12].

In the study, age was similar in vitamin D deficient and normal vitamin D groups. Accordingly, Erkus et al. found no age difference between vitamin D deficient and normal vitamin D groups [13]. However, previous works reported that older subjects tend to have vitamin D deficiency more than younger adults [14,15]. Exposure to sunlight, in which the territory where the study conducted received enough sunlight, may explain the similar ages within the Vitamin D deficient and normal Vitamin D groups. Another factor could be a relatively small study cohort. Finally, the study population consisted of patients with T2DM. This disorder is more prevalent in elderly; therefore, young subjects with higher Vitamin D levels were excluded if they were not diabetic.

In a study by Afzal et al., which examined all previously published prospective studies in Denmark, it was stated that the risk of developing T2DM in those with vitamin D deficiency was 1.5 times higher than in the vitamin D normal group [16]. Similarly, in a study by Chiu et al., it was reported that vitamin D inadequacy increased the incidence of metabolic syndrome and is negatively related to serum vitamin D levels, insulin sensitivity, and beta cell function, thus making it a risk factor for the insulin resistance seen in T2DM and metabolic syndrome [17]. According to the reported meta-analysis results of eleven prospective studies included in the EPICNorfolk (European Prospective Investigation into Cancer) study, in which a population of 3600 people was followed, there was a proportionally negative relationship between serum 25(OH)D3, the incidence of T2DM, and vitamin D supplementation was associated with a reduced risk of T2DM [18]. Serum vitamin D levels were generally found to be insufficient in our study population. In our study, the median value of the low vitamin D group was 12.7 ng/mL in patients diagnosed with T2DM, while the median value was found to be 28 ng/mL in the normal vitamin D group [18].

There are studies in the literature that support a relationship between vitamin D levels and age and gender [19]. In a study conducted by Lips, it was stated that the serum vitamin D levels were lower in women compared to men [20]. In Baker et al.'s study, which included women aged 20-96, it was reported that the average serum vitamin D level decreased with age, and abnormally low levels of vitamin D were detected in the elderly population [21]. Neither the age nor the gender of the participants in the normal vitamin D and low vitamin D groups were different in present study. Additionally, in our study, no significant difference was observed between the groups with low and normal vitamin D in terms of anthropometric measurements such as height, weight, waist circumference, and hip circumference. However, there were also studies in the literature that pointed out that the body mass index (BMI) value was significantly higher in the group with vitamin D deficiency than in individuals with normal vitamin D levels [7].

According to a recent published work, normal vitamin D levels reduce the risk of developing T2DM [22]. In another study, it was found that patients diagnosed with diabetes and vitamin D deficiency had higher HbA1c levels compared to the normal vitamin D group [23]. In our study, the median HbA1c value was found to be higher in the group with vitamin D deficiency compared to the other group. In this context, an inversely proportional relationship between vitamin D and HbA1c was detected in our study.

In another study conducted in China with 1475 participants, it was shown that the TG value in male individuals with vitamin D deficiency was higher than in men with normal vitamin D levels [24]. Goldberg stated that as a result of uncontrolled T2DM, there may be an increase in TG, and therefore total cholesterol levels along with hyperglycemia [25]. In the present study, the median value of TG, which is one of the serum lipid parameters, was higher in the vitamin D deficient group, similar to the literature. Additionally, in our study, a significant negative

correlation was observed between vitamin D and serum TG values. Moreover, it was determined that there was a directly proportional correlation between FBG and TG.

In recent years, research has focused on some new and practical ratios used in the diagnosis and prognosis of many conditions associated with inflammation. Among the hemogram parameters, hemogram-derived parameters such as the WBC, NLR, PLR, MLR, and inflammation markers produced from peripheral blood such as the serum CRP value attracted the attention of researchers in terms of the prognosis of systemic inflammatory diseases, and new literature studies are in this direction [26]. Many studies in the literature have stated that inflammation induced by immune system cells is related to insulin resistance and T2DM, and that CRP levels are higher in patients diagnosed with diabetes who had low levels of vitamin D compared to healthy individuals [27]. The results of Chen et al.'s meta-analysis of 10 studies consisting of 924 participants indicated that vitamin D supplementation significantly reduced circulating CRP levels [28]. However, in our study, no significant difference was observed in terms of the CRP levels between groups with deficient serum vitamin D levels and those with normal serum vitamin D levels. Since our entire study population consisted of individuals diagnosed with T2DM and the inflammatory burden was valid for all patients diagnosed with T2DM, we found no significant difference between the groups in terms of the CRP levels.

Vitamin D levels may be correlated with the control level of T2DM, one of the metabolic diseases, as discussed above, and it has been noted in studies that it is associated with high serum inflammatory marker levels and hemogram and hemogram-derived parameters, which are also associated with inflammation [7]. In a study that examined the vitamin D levels of premenopausal women with iron deficiency anemia, it was stated that the Hb value was significantly lower in the low vitamin D group than the normal group [29]. The NLR level has been associated with other inflammatory conditions. For example, as increased NLR level was reported in patients with irritable bowel disease [30]. In our study, remarkable results were obtained between vitamin D levels, Hb levels, and NLR values in individuals diagnosed with T2DM. In our study, Hb levels were found to be lower in the T2DM diagnosed group with low vitamin D levels compared to the group with normal vitamin D levels. Additionally, in our study, a significant positive correlation was observed between the NLR and the HbA1c levels.

The present study has some limitations, including the following: retrospective design of the study, relatively small study cohort, and a single center nature of the study are among those limitations. However, to the bets of our knowledge, both an increased NLR level and low serum levels of vitamin D were found to be associated with poor diabetic control in the present study. These markers can be used in clinical practice as helpful markers to assess diabetic control.

5. Conclusions

In conclusion, in our study, an association was observed between low vitamin D levels and poor diabetic control in patients with T2DM. Moreover, NLR was associated with the diabetic control level. The ease to assess and the inexpensive nature of these indices make them helpful in follow up of the T2DM patients with a vitamin D deficiency.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Informed consent

Written informed consent was approved from all participants in the study.

Ethical approval

This study was approved by Abant Izzet Baysal University Ethics Committee (approval date: 8th of March, 2022; approval number: 2022/53).

Conflict of interest

The authors declare no conflict of interest.

Author's contributions

Study design: Elif Basaran, Gulali Aktas; data curation: Elif Basaran; formal analysis: Elif Basaran, Gulali Aktas; data interpretation: Elif Basaran, Gulali Aktas; statistical analyses: Gulali Aktas; writing first draft: Elif Basaran; critical review and writing of the manuscript: Gulali Aktas.

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