



## **Effect of Vitamin D Supplementation on Serum Lipids, Uric Acid and C-reactive Protein in Patients with Type II Diabetes Mellitus**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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### **ABSTRACT**

**Background:** Type II Diabetes Mellitus (T2DM) is a considerable problem of global health, and finding new therapies for treating the disease continues. Recently, attention has been focused on vitamin D as a potential lowering agent of T2DM's risk factors and its complications. The present work was conducted to determine the effect of vitamin D supplements on serum lipids, uric acid, C-Reactive Protein (CRP) and also Homeostatic Model Assessment of Insulin Resistance (HOMA-IR).

**Materials and Methods:** Sixty patients with T2DM as well as deficiency of vitamin D and referred to Rasoul-e-Akram Hospital in 2017 were selected by convenience sampling method. To begin the study, patients' demographic information was required, so a questionnaire including age, waist circumference, sex, height, blood pressure and weight was provided. Patients with vitamin

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D3<30ng/ml were treated by a daily oral dose of 2000 unit of vitamin D supplementary for 12 weeks. Serum levels of triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), total cholesterol (TC), fasting blood sugar (FBS) and Hemoglobin A1C (HbA1C) were measured before and after vitamin D intake. Analysis of data was carried out through the Software Package SPSS Ver. 24.

**Results:** Sixty-five percent of study population (39 people) was composed of females. The mean value  $\pm$  standard deviation (SD) amount of age and BMI were  $46.8 \pm 8.9$  years and  $28.4 \pm 4.3$  m<sup>2</sup>/kg. The mean  $\pm$  SD systolic blood pressure (SBP),  $19.3 \pm 122.8$  mmHg and diastolic blood pressure (DBP) were  $14.1 \pm 79$  mmHg. The mean  $\pm$  SD of vitamin D in patients was  $11.4 \pm 4.5$  ng / ml. The comparison of blood factors before and after treatment showed p value > 0.05.

**Conclusions:** Deficiency of vitamin D should be treated and prevented, but administration of this high-dose vitamin D supplements for prevention or improvement of T2DM has not been recommended yet. Our study showed a correlation between the vitamin D intake and decreased level of FBS and Uric Acid in diabetic patients.

*Keywords: Diabetes mellitus; vitamin D; uric acid.*

## 1. INTRODUCTION

Type II Diabetes Mellitus (T2DM) has found a growing prevalence in the community and the long term consequences of diabetes and other risk factors including hyperlipemia, hypertension, etc. can exacerbate the complications of T2DM, and on the other hand, the prevalence of deficiency of vitamin D appears to be high in all communities [1]. Besides, T2DM is a major global health problem, and the development of new drug therapies for its treatment continues. Because of the increasing burden of T2DM on the community health system, there is a need for urgent action on innovative approaches for prevention of diabetes progression and the related complications. Recently, attention has been given to vitamin D as a probable reducer of the potential risk of T2DM and its complications [2].

The vitamin D importance in the natural functioning of many body systems, including skeletal muscle, immune system and cell proliferation, the treatment of many autoimmune diseases, and so on is proved strongly. Vitamin D has been shown to have beneficial effects in many inflammatory diseases and there is evidence that Vitamin D reduces the risk of various types of internal malignancies, in addition to its classic physiologic effects on calcium metabolism and bone homeostasis [3]. Vitamin D has been found to be an important factor for maintenance of the normal function of several non-skeletal tissues including immune function, muscle as well as cellular proliferation and differentiation. Deficiency of vitamin D may increase the risk of type I and II diabetes

mellitus, high blood pressure, insulin resistance, asthma and depression [4].

Although the minimum daily vitamin D intake in adults exposed to sunlight is not well known, consumption of less than 0.2 mg per day (i.e. 80 units per day) is associated with deficiency in adults [3,5]. National Academy of Sciences (NAS) recommends a vitamin D content of 15 mg/day and 20  $\mu$ g/day for younger than 70 and older than 70 individuals, respectively. This daily needed content can be provided through the consumption of fortified foods, sun exposure or a vitamin D supplement [4].

In addition, the active metabolite of vitamin D can promote  $\beta$  cell's differentiation and growth. Deficiency of vitamin D causes secondary hyperparathyroidism and high concentrations of parathyroid hormone (PTH) may cause glucose intolerance [6]. The link between insulin resistance and deficiency of vitamin D can be caused by inflammation because deficiency of vitamin D is accompanied with increased inflammatory markers [5]. However, a study was conducted to find a relationship between C-reactive protein and vitamin D, where no evidence of a causal relationship was found [7].

The correlation between levels of vitamin D and lipid profiles remains unclear [8]. Some epidemiological studies indicate an inverse relationship between 25(OH)D circulating levels and cardiovascular events biomarkers [9]. However, some studies found no evidence on positive effect of vitamin D supplements on lipid profile improvement [10]. As once mentioned HOMA-IR (which stands for Homeostatic Model Assessment for Insulin Resistance) is a

mathematical approach and a powerful clinical and epidemiological tool for evaluating Insulin Resistance (IR) [11]. Few studies have been undertaken to investigate the relationship between HOMA-IR and vitamin D, which have shown different results [12-13].

The impact of vitamin D on fat amount and cardiovascular diseases has been examined by several researchers through randomized control studies. In a research for evaluation of the impact of vitamin D on serum lipid levels in patients with T2DM, the levels of serum 25(OH)D were inversely correlated with levels of triglyceride, while no correlation was found between those of 25(OH)D, LDL, VLDL and HDL [14]. The positive impact of vitamin D on harmful lipids was also found in the Cutillas-Marco study, where a negative relationship between vitamin D and TC ( $P=0.01$ ) and LDL ( $P=0.04$ ) was shown, as well [15].

The causative relationship between vitamin D deficiency, T2DM and its associated complications should be proved by interventional studies showing improved insulin sensitivity and other parameters involved in diabetes complications, using vitamin D supplements. Studies in this area have been carried out in different regions with conflicting results. Given the increasing attention to vitamin D and lack of definitive results in this area, this study aimed at investigation of the effects of administration of vitamin D supplements on serum lipids, uric acid, CRP and HOMA-IR.

## 2. METHODS

The present study is a clinical trial. The statistical population was composed of all patients with T2DM and deficiency of vitamin D referring to Rasoul-e-Akram Hospital in 2017. To this end, following to convenience sampling method, 60 T2DM patients diagnosed to have deficiency of vitamin D were chosen. They were given a demographic and personal information questionnaire. Also, BMI, height, weight, blood pressure and waist circumference were measured by a general practitioner.

### 2.1 Exclusion Criteria

The exclusion criteria included pregnancy, breastfeeding, taking effective drugs on lipid profile/ calcium, vitamin D and bone metabolism, chronic liver or kidney disorders, endocrine disorders such as hypo or hyperthyroidism and

hyperparathyroidism, smoking, taking anticoagulants and vitamin D or calcium supplements.

### 2.2 Procedure

To evaluate lipid profile changes (including HDL, TG, TC and LDL), FBS, HbA1C, Uric Acid, CRP and HOMA-IR before and after treatment with vitamin D3, baseline and final levels of these factors were required to provide the conditions for comparison and analysis. Also, by measuring vitamin D3 levels, those who had inadequate levels of vitamin D3 were excluded from the study. Therefore, before starting treatment with vitamin D3, the serum samples were taken to measure lipid profile (including HDL, TG, TC and LDL), FBS, HbA1C, Uric Acid, CRP and HOMA-IR. Samples were sent to the laboratory of Rasoul-e-Akram Hospital within 20 minutes from venipuncture. In this laboratory, HDL, TG, TC, LDL, FBS and uric acid were determined by spectrophotometry method, and HbA1C and CRP were examined by nephelometry. After this stage and recording the baseline serum levels of these factors, the patients' treatment by vitamin D3 was started; to this end, patients with Vit D3<30IU/ml were treated with oral vitamin D3 at a daily dosage of 2000IU. 12 weeks after onset, the above tests were performed again and the information was analyzed in the platform of SPSS software, and the values were compared to baseline values.

### 2.3 Analysis

Mean and standard deviation were used for quantitative variables, and ratio as percent was reported for qualitative variables. In case of normal distribution (measurement using K-S test), paired t-test was used before and after treatment; otherwise, the non-parametric equivalent test (Wilcoxon signed-rant test) was employed.

## 3. FINDINGS

In the 60 subjects participated in present study, 39 patients (65%) were females and 21 ones (35%) were males. Other demographic and general medical results obtained from questionnaire and examination is summarized in Table 1.

As it can be seen from Table 1, the subjects were in the age range of 27-75, whose mean age

was  $46.8 \pm 8.9$ . In terms of BMI, their mean BMI value was  $28.4 \pm 4.3 \text{ kg/m}^2$  in the range 20.1-40.8. Besides, the mean waist circumference of subjects was  $96.9 \pm 9.3 \text{ cm}$  in the range 81-124 cm. The mean Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) were  $122.8 \pm 19.3 \text{ mmHg}$  (in the range 90-170 mmHg) and  $79 \pm 14.1 \text{ mmHg}$  (in the range 60-130 mmHg), respectively. Also, the highest frequencies were 130 mmHg and 70 mmHg for SBP and DBP, respectively. Finally, the patients mean vitamin D content was  $11.2 \pm 4.5 \text{ ng/ml}$  in the range 4-24 ng/ml.

On the other hand, the results of evaluations conducted on participants' blood sample and FBS, HbA1C, TC, TG, HDL, LDL, CRP, Uric Acid and HOMA-IR are briefly presented in Table 2

according to before and after intake of vitamin D supplementary.

Fig. 1 depicts a comparative diagram of the participants' FBS before and after the Vitamin D intake.

In addition, Fig. 2 shows a comparative diagram of the participants' TC before and after the Vitamin D intake.

Furthermore, Fig. 3 presents a comparative diagram of the participants' TG before and after the Vitamin D intake.

Moreover, Fig. 4 depicts a comparative diagram of the participants' HDL before and after the Vitamin D intake.

**Table 1. Demographic and general variables measured in the participants**

Variable	Mean	Standard deviation
Age (years)	46.8	8.9
BMI* ( $\text{kg/m}^2$ )	28.4	4.3
Waist circumference (cm)	96.9	9.3
SBP** (mmHg)	122.8	19.3
DBP*** (mmHg)	79	14.1
Vitamin D (ng/ml)	11.2	4.4

\* Body Mass Index

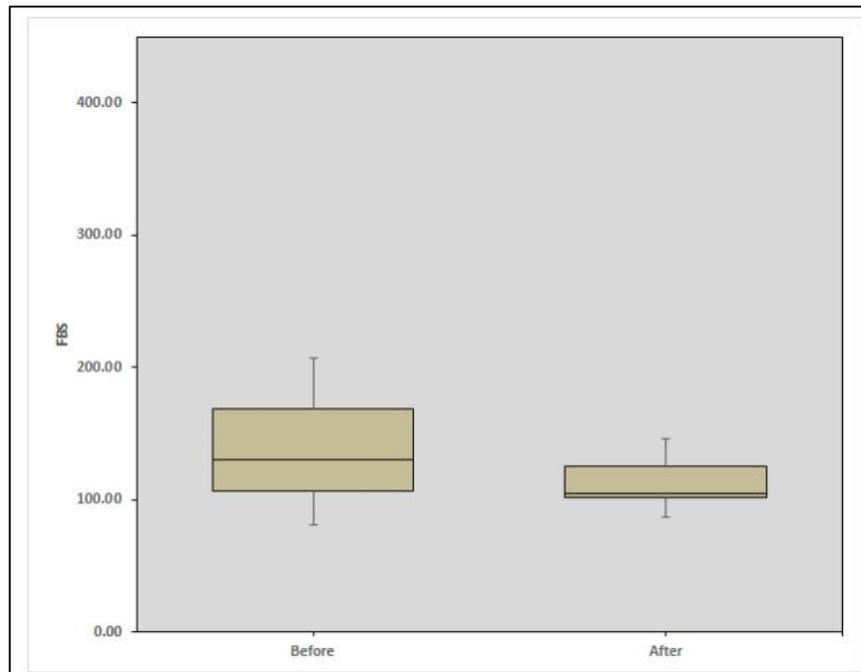
\*\* Systolic Blood Pressure

\*\*\* Diastolic Blood Pressure

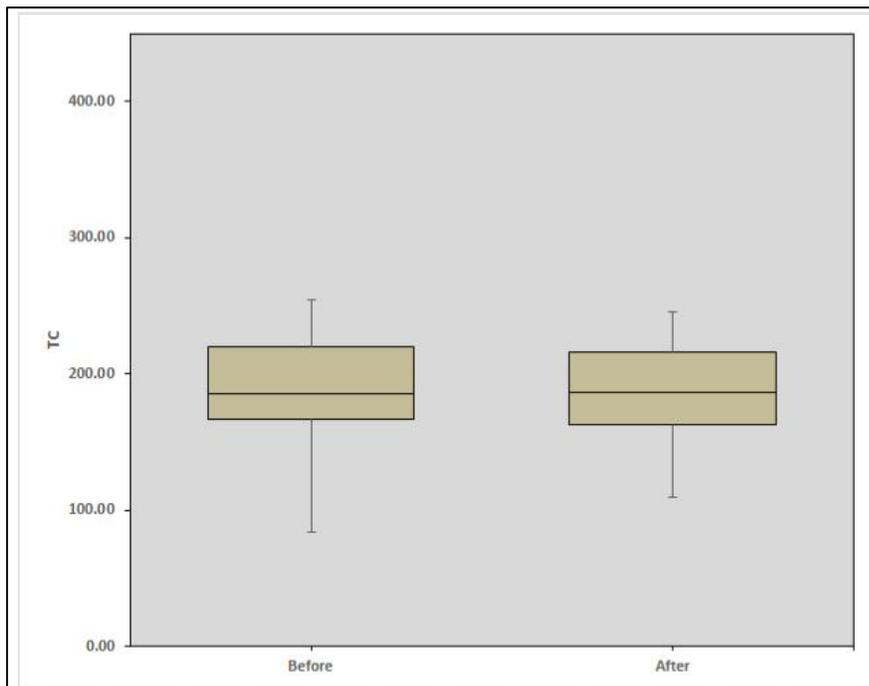
**Table 2. The blood factors measured before and after intake of vitamin D supplementary**

Variable	Phase	Mean	Standard deviation	Min	Max	P-Value
FBS (mg/dl)	Before	148.6	61.1	80.5	359.2	0.011
	After	128.7	45	87.5	444	
HbA1C (%)	Before	7.7	1.2			0.19
	After	7.2	1.1			
TC (mg/dl)	Before	193.7	43.6	84	307	0.29
	After	187	36	110	266	
TG (mg/dl)	Before	188.8	93.07	60	467	0.47
	After	165	82	45	456	
HDL (mg/dl)	Before	39.6	7.6	25.5	54.5	0.052
	After	38.7	5.8	15.3	77	
LDL (mg/dl)	Before	111.9	28.2	35	193.8	0.24
	After	114	28.1	59	174	
CRP (mg/dl)	Before	8.9	2.3	4.1	16.2	0.25
	After	6.5	1.8	3.9	13.5	
Uric Acid (mg/dl)	Before	5.1	1.3	2.99	9.7	0.001
	After	4.6	1.2	2.44	6.8	
HOMA-IR	Before	4.9	2.4	0.6	12.7	0.087
	After	4.1	2.1	0.77	19.39	

*Fasting blood glucose (FBS), C-reactive protein (CRP), Serum levels of triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), total cholesterol (TC), fasting blood sugar (FBS) and Hemoglobin A1C (HbA1C)*



**Fig. 1. The participants' FBS before and after the Vitamin D intake**



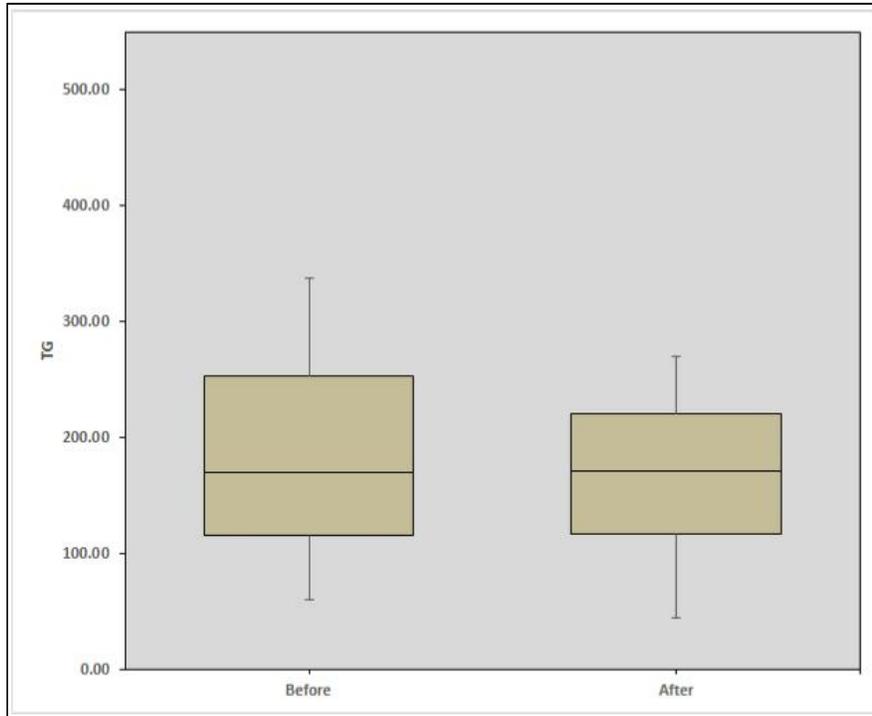
**Fig. 2. The participants' TC before and after the Vitamin D intake**

Additionally, Fig. 5 provides a comparative diagram of the participants' LDL before and after the Vitamin D intake.

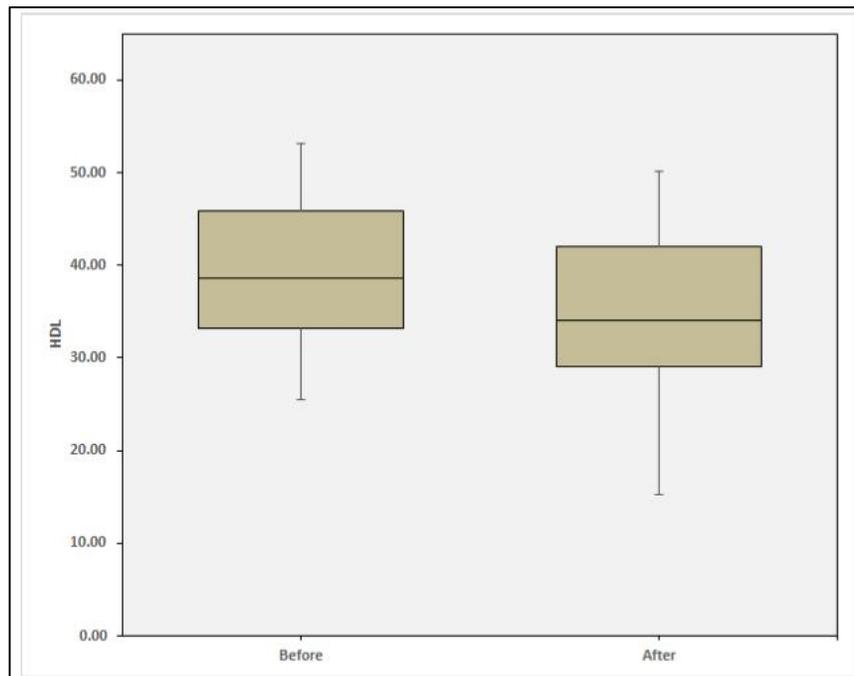
Besides, Fig. 6 provides a comparative diagram of the participants' CRP before and after the Vitamin D intake.

Meanwhile, Fig. 7 provides a comparative diagram of the participants' Uric Acid before and after the Vitamin D intake.

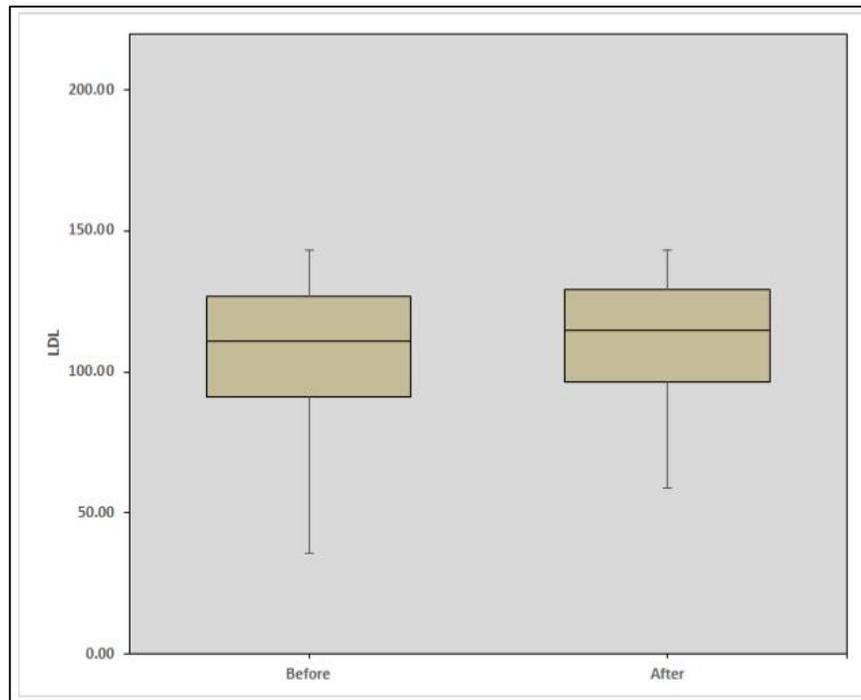
Finally, Fig. 8 provides a comparative diagram of the participants' HOMA\_IR before and after the Vitamin D intake.



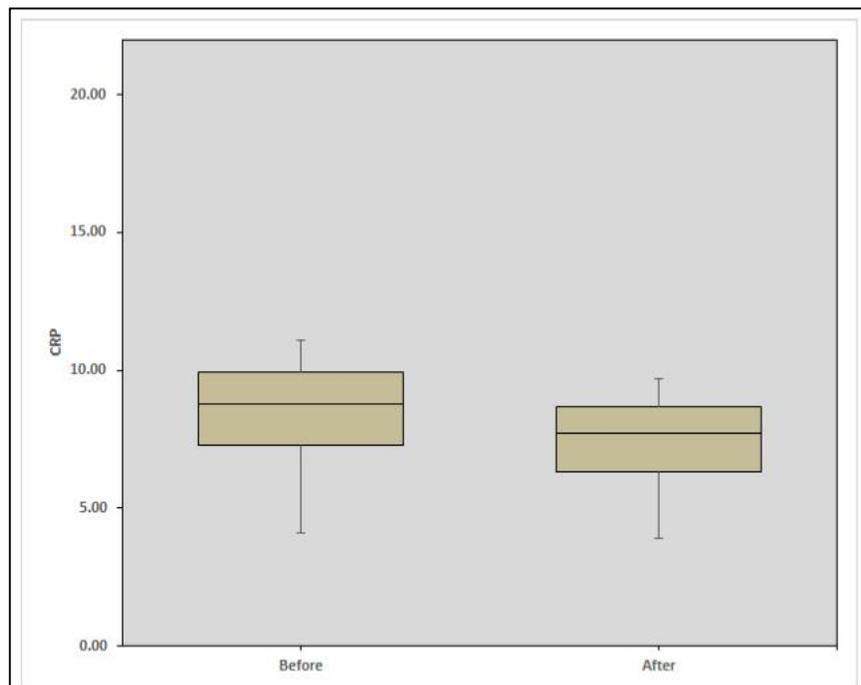
**Fig. 3. The participants' TG before and after the Vitamin D intake**



**Fig. 4. The participants' HDL before and after the Vitamin D intake**



**Fig. 5. The participants' LDL before and after the Vitamin D intake**



**Fig. 6. The participants' CRP before and after the Vitamin D intake**

Meanwhile, normality evaluation was performed by K-S test on Table 2 variables except LDL, HDL and HOMA-IR variables that were normal,

all other variables did not follow normality. Paired-t test and Willcoxon test were used on normal and abnormal variables, respectively, to

compare mean data before and after vitamin D supplementation. Comparison of blood factors before and after treatment showed p-

value<0.05 for FBS and Uric Acid and p-value>0.05 for TG, T-CHOL, LDL, HDL and HOMA-IR.

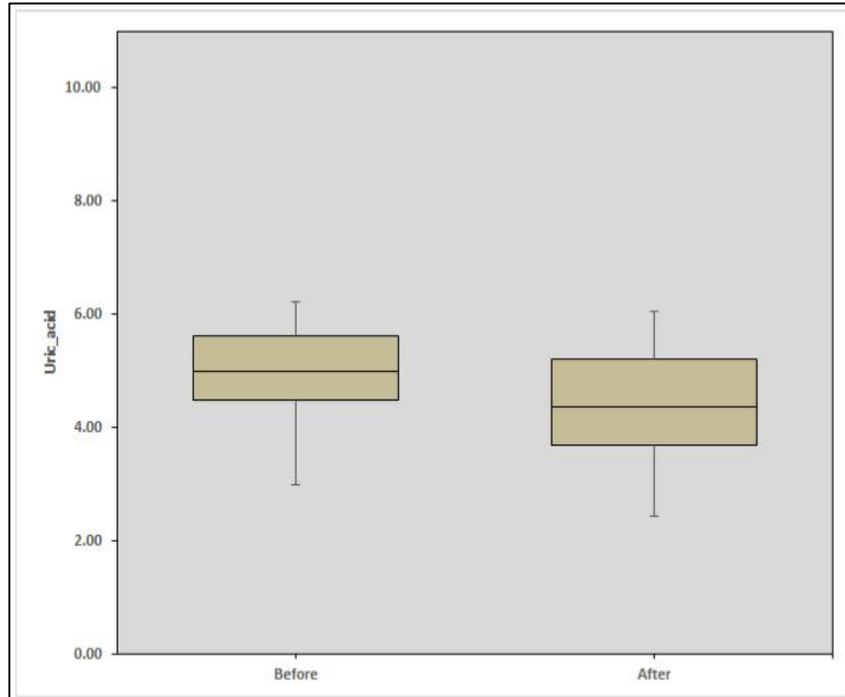


Fig. 7. The participants' uric acid before and after the Vitamin D intake

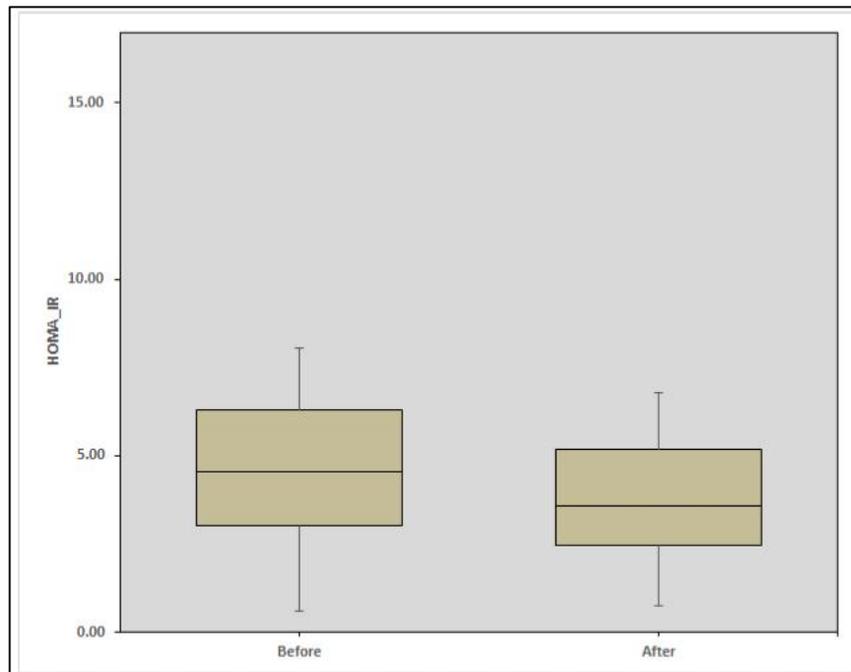


Fig. 8. The participants' HOMA\_IR before and after the Vitamin D intake

#### 4. DISCUSSION

There is growing evidence that vitamin D holds a key and crucial contribution in eliminating the risk of developing T2DM and the corresponding complications. In this regard, vitamin D leads to both direct and indirect effects. One of the indirect effects of vitamin D can be on the different mechanisms involved in the pathophysiology of T2DM, including the function of pancreatic cells and insulin, through regulating calcium levels. Human evidence is mainly obtained through prospective cross-sectional and observational studies [2]. According to some studies, deficiency of vitamin D has been correlated with reduction of insulin release, insulin resistance, and T2DM [16]. Animal studies indicate that  $1,25(\text{OH})_2\text{D}_3$  stimulates insulin secretion from the pancreatic beta cell [17].

The correlation between deficiency of vitamin D and insulin resistance can be established based on inflammation, as some studies have suggested that deficiency of vitamin D is correlated with inflammatory markers' increase [18]. Additionally, vitamin D-related genes' genetic polymorphisms may lead to impair control of blood glucose and thus catching T2DM [17]. Some epidemiological studies have shown a link between a decrease in serum  $25(\text{OH})\text{D}_3$  concentration and an increased risk of suffering from metabolic syndrome and T2DM [19].

The results of this study showed no relationship between vitamin D supplementation and lipid profile level, FBS, uric acid and HOMA-IR in patients with T2DM and deficiency of vitamin D.

Ford, et al. [18] found a negative relationship between TG and  $25(\text{OH})\text{D}$  in patients suffering from hypertriglyceridemia. However, such a relationship was not seen regarding HDL in healthy subjects. In a study by Chiu, et al. [19], no relationship is reported between serum  $25(\text{OH})\text{D}$  level and TG or HDL in healthy individuals.

In the Third National Health and Nutrition Examination Survey (NHANES III) conducted on 6228 persons, people with  $25(\text{OH})\text{D}$  levels  $\geq 81$  nmol/l showed the lowest rate of catching T2DM. The OR for diabetes was 0.25 for non-Spanish whites and 0.17 for Mexican-Americans compared to those with  $25(\text{OH})\text{D} \leq 43.9$  nmol/L [20].

The correlations between vitamin D status and blood glucose which were observed in epidemiological investigations, should be demonstrated using randomized double-blind clinical trials in order to establish a validated scientific relationship. Accordingly, above 30 clinical trials were carried out in both normal population and patients with pre-diabetic, T2DM, and gestational diabetes or a combination of these. At least 14 cases of these studies were for patients with T2DM. The findings of such clinical trials regarding the effect of vitamin D compared to placebo, occasionally with calcium, have been inconsistent to date [6].

In a study conducted by Tromsö, et al. [21], 36 patients suffered from T2DM and treated with metformin and insulin were randomly assigned to receive either the supplementation 000 IU/wk, Vit D3 40 or placebo for 6 months, which ultimately no significant effect on glucose metabolism was observed.

In a clinical trial study in Germany on 86 T2DM patients, the relationship between 1904 IU/d of vitamin D or placebo was evaluated in these subjects, indicating that vitamin D effects metabolic parameters. However, HbA1c content was lower in those with  $25(\text{OH})\text{D} > 50$  nmol/l compared to subjects with  $25(\text{OH})\text{D} < 50$  nmol/l [22].

In a cohort study initiated in England in 1958, a strong negative relationship was found between HbA1c and  $25(\text{OH})\text{D}$ . When HbA1c levels in subjects with serum level of  $25(\text{OH})\text{D} < 25$  nmol/l were compared to those having serum levels of  $25(\text{OH})\text{D} > 75$  nmol/l, it was concluded that HbA1c was lower in the second group (5.37% versus 12.5%), and even this difference was more pronounced in obese individuals [23].

In an Australian double-blinded study on fifty patients newly diagnosed with T2DM, the subjects were chosen randomly to receive 6,000 IU/d of vitamin D or placebo. In these subjects, FBS levels improved slightly after 3 months of continuous supplementation. The subjects returned to initial mode after 6 months [24]. In another study undertaken in UAE, 87 obese patients with T2DM and deficiency of vitamin D were treated with vitamin D supplementation of 6000 IU/d for 3 months, and then they divided into two groups receiving either placebo or vitamin D 3000IU/d. After 6 months of the second step of measurements, indifference was seen in HbA1C, FBS, BP and C-peptide before and after vitamin D treatment [25].

In a Swiss study, vitamin D3 was randomly administered for 55 patients with T2DM. It was IU 300,000 which was applied on muscle or placebo. HOMA-IR and HbA1c were improved in group receiving Vitamin D [12].

However, the reason for the ineffectiveness of vitamin D supplementation may be the low dose or short duration of administration. Furthermore, studies have been conducted to rule out this issue, in which high doses and long doses of vitamin D (even up to several years) were studied, with conflicting results.

## 5. CONCLUSION

Overall, there is no clear and precise correlation between vitamin D supplementation and improvement in lipid, glucose, and inflammation profiles in T2DM patients. Our study showed a p-value<0.05 for FBS and Uric Acid and p-value>0.05 for TG, T-CHOL, LDL, HDL and HOMA-IR before vitamin D intake and after treatment. There was insignificant relationship between vitamin D intake and improvement of FBS levels in diabetic subjects. However, no significant relationship was found between vitamin D intake and improvement of FBS and Uric Acid levels. In addition, an insignificant relationship was also seen between Vitamin D intake and improvement of CRP, HDL, TG, T-CHOL, LDL, HOMA-IR and HbA1C. Finally, deficiency of vitamin D should be treated and prevented, but high-dose administration of this vitamin is not recommended to prevent or eliminate T2DM.

## CONSENT AND ETHICAL APPROVAL

As per university standard guideline, participant consent and ethical approval have been collected and preserved by the authors.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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