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COMPARITIVE STUDY TO ASSESS THE EFFECT OF VITAMIN D3 SUPPLEMENTS IN HYPERLIPIDAEMIC AND TYPE 2 DIABETES PATIENTS

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ABSTRACT:
Diabetes mellitus is now considered as major metabolic disorder and the Vitamin D is also associated with the occurrence of Diabetes mellitus. Vitamin D levels are linked to high blood pressure, neoplastic, and heart disease. A deficiency of vitamin D is linked with the development and progression of diabetes. Although there is an association between vitamin D and insulin secretion, insulin resistance, and beta cell dysfunction in patients with diabetes, the evidence on vitamin D levels and DM is conflicting and poorly controlled. There is increasing evidence that deficiency is a risk factor for diabetes and chronic kidney disease, but it is not clear regarding the death of diabetic patients due to vitamin D deficiency Currently, vitamin D supplementation has not been shown to improve glycaemic control or prevent the development of diabetes, but with adequate sample size, study duration, and optimal dose of vitamin D supplementation, further clinical trials are needed. In this article major scenario shown on the mechanisms of primary vitamin D deficiency associated with Diabetes Mellitus, and describes the recent evidence on vitamin D medication in patients with these diseases.

Keywords: Diabetes mellitus; Vitamin D supplement, Vitamin D deficiency

1. INTRODUCTION

INTRODUCTION:

1.1 Type 2 Diabetes

Type 2 diabetes is the most widely recognized kind of diabetes, representing around 90%, of cases of all diabetes. Hyperglycemia is caused by inadequate of insulin synthesis and the body's inability to respond entirely to insulin, which is known as insulin resistance in type 2 diabetes. Insulin resistance causes insulin to be inefficient, which causes a rise in insulin output to lower rising glucose levels. However, with time, a state of relative insufficient insulin production can evolve. Type 2 diabetes is more common in older adults, although it is becoming more common in teenagers and younger adults as obesity, physical inactivity, and poor diet become more prevalent. Increased thirst, excessive urination, tiredness, slow healing wounds, chronic infections, and tingling or numbness in the hands and feet are all signs of type 2 diabetes. While the causes of type 2 diabetes

are unknown, there is a clear correlation with overweight and obesity, as well as rising age, race/ethnicity and family disease background. Abdominal obesity, inadequate diet and nutrition (including sugar-sweetened substances), physical inactivity, prediabetes or impaired glucose tolerance (IGT), smoking, and a previous history of Gestational Diabetes (GDM) are also modifiable risk factors of type 2 diabetes mellitus.[1] Diagnosis of type 2 diabetes mellitus is very much complex and is still in worldwide debate. However, IDF recommends the following criteria for diagnosis of diabetes. Diabetes should be diagnosed if one or more of the following criteria are met: "Fasting plasma glucose ≥126mg/dl;2 hour plasma glucose ≥200mg/dl following a 75 g of oral glucose load; A random glucose>200mg/dl or Glycated haemoglobin (HbA1c) level ≥6.5%". Diabetics are most likely to have cardiovascular disease (CVD). Cardiovascular diseases (CVDs) are a constellation of syndromes of the heart and blood vessels which include coronary heart disease, cerebrovascular disease, peripheral arterial disease. High blood glucose levels can trigger the blood coagulation system, raising the risk of blood clots. Diabetes is linked to elevated blood pressure and cholesterol, which raises the likelihood of cardiovascular risks including angina, coronary artery disease (CAD), myocardial infarction, stroke, peripheral artery disease (PAD), and congestive heart failure. In 2016, the International Diabetes Federation (IDF) released a systematic study on diabetes and cardiovascular disease epidemiology. People with diabetes are 2 to 3 times more likely to have cardiovascular disease (CVD) than people without diabetes. CVD prevalence rises with age and varies by country, with higher prevalence in low- and middle-income countries relative to high-income countries.[2]

NEED OF THE STUDY.

According to survey report which revealed that approximately 85% of population have vitamin D deficiency. The study reported that overall, 62.8% had obesity,42.8%had high BP,18.2% had high FPG, 48.8% had low HDL, 14.2 % had high TG in local population. These reports encouraged us to conduct the study among Rajasthani ethnic group of Jaipur region for the effect of vitamin D supplementation on cardiometabolic disorders in Hyperlipidaemic and Type 2 Diabetes Patients.

According to the reports of International Diabetes Federation 2017, Diabetes and Cardiovascular diseases are top 10 causes of death globally. South Asian countries like India and China are very much affected due to this. Considering this fact, if left untreated or progresses, this disease may cause huge socioeconomic burden in India. So, new approach of treatment aspects is necessary to prevent the growth of cardiometabolic disorders.

Animal studies provide strong evidence that vitamin D is inversely related with cardiometabolic disorders. So, literature reports indicates that by improving vitamin D status may be helpful in treating these diseases. Up to date, clinical trials have been conducted to study the effect of vitamin D supplementation on cardiometabolic disorders but results from the trials were found to be inconsistent.[49]

Despite of the strong findings of correlation between vitamin D and cardiometabolic disorders, interventional studies have not found any sufficient evidence to clarify the link between vitamin D and cardiometabolic disorders. Therefore, there is lack of evidences for the effect of vitamin D on the Hyperlipidaemic and Type 2 diabetes patients and also causality relationship between vitamin D and Hyperlipidaemic and Type 2 diabetes patients is not evident.

So, systematic clinical study is warranted. However, researchers reported great potential of vitamin D supplementation in treating patients with Hyperlipidaemic and Type 2 diabetes patients. Moreover, one study reported that there was variation in the effect of vitamin D as per the race/ethnicity group.

Therefore, we have selected the Rajasthani ethnic group those residing at Jaipur, Rajasthan, India. Till date, clinical study for the effect of vitamin D supplementation in the patients of Rajasthani ethnicity with in Hyperlipidaemic and Type 2 diabetes patients is not yet been conducted at Rajasthan.

RESEARCH METHODOLOGY

STUDY DESIGN AND METHODOLOGY

Study Design Study design was a prospective and comparative analysis

Sample Size Estimation: Total sample size was 124 subjects for both groups.

Estimated sample size was calculated by substituting the following formula:

$$S = (z)^2\, p\,(1 - p) / m^2$$
$$= (1.44)^2 0.5(1\text{-}0.5)^2/0.05^2$$

n = estimated sample size, m= level of significance of 5% (0.05), p= level of confidence -1.44 (power is 85%), the estimated predicted difference between the two mean values of the 2 groups and estimated to be 0.5

Study Duration: 3 months

- **Randomization:** By using a randomization procedure, 62 patients in the vitamin D group got vitamin D supplementation (cholecalciferol), whereas another 62 patients in the non-vitamin d group did not get cholecalciferol (Control group)

Inclusion Requirements

- They ranged in age from 18 to 75 and belonged to the Rajasthani ethnic group of the Jaipur area.
- They underwent testing to check for vitamin D levels below 12 ng/ml (vitamin D deficiency level)
- Patients were of Hyperlipidemic and Type 2 diabetes patients which includes "fasting blood triglycerides (TG) ≥ 150 mg/dl. High density Lipoprotein level(HDL) < 40 mg/dl in males and 102cm in males or >88 cm in females" and fasting blood glucose level above 150 mg/dl.

Exclusion Criteria

- If a subject had "known history of type 1 diabetes mellitus, they were excluded from the study.
- Patient with primary hyperparathyroid disorders, hypercalciuria, nephrolithiasis, sarcoidosis, and Paget's disease.
- Pregnant women and dialysis patients were also excluded from the trial.

Choosing a dosage

The maintenance dose of cholecalciferol was administered once a month for six months after the loading dose of 60,000 IU/week (p.o.) for four weeks.

Study Design

At the time of screening, respondents' demographic information—including age, gender, and ethnicity—as well as their medical history of illnesses were collected. Heart disease, diabetes mellitus, hypertension, renal, bone, and joint issues were all noted in the past. At visit 1 of the first month, randomization was conducted. Patients had follow-up twice, at 45 and 90 days.

Measurement and analysis of blood sample

Through the use of a mercurial sphygmomanometer, blood pressure was measured.

We measured weight using calibrated weighing scales.

The waist circumference was measured using measuring tape.

Patients were requested to give a blood sample after an overnight fast of at least 8 to 12 hours. Blood was drawn using a sterile needle, and then submitted to the lab for examination. Two hours after consuming 75g of anhydrous sugar, a second blood sample was taken to measure the postprandial blood glucose (PPBG) level. On a fully automated biochemistry analyzer, blood serum was utilised for the analysis of total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C), while blood plasma was used for the measurement of glucose concentration.

Evaluation by visit

Patients in both groups underwent a total of 3 visits during the trial.

Visit 1 (0 Month)

Subjects were allocated to the vitamin D group and the non-vitamin D group after being informed about the study. Then, for both groups, demographic information, concurrent medications, as well as a medical history of cardiometabolic illnesses, were noted.

Data from the two groups were collected after the individuals completed the questionnaires. SBP/DBP and HR physical exams were conducted on the participants in both groups, and results were recorded. From the patients in both groups, 5ml of blood was taken for clinical laboratory tests (lipid profile, fasting blood glucose, postprandial blood glucose, HbA1c, and 25(OH)D level).

Patients in the vitamin D group received nine supplements of cholecalciferol in accordance with the recommended dosage.

Patients in the vitamin D group were given subject diaries to keep track of their drug compliance, and every month, hospital staff would call patients to remind them to take their medications. Patients in the non-vitamin D group underwent follow-up through telephone or hospital visit. Both groups' subjects had a second visit scheduled for 45 days later.

Visit 2 (At 1 and half months)

Patients in the vitamin D group evaluated subject diaries for dose compliance. Following that, concurrent drugs from the vitamin D group were evaluated, and additional medications from the non-vitamin D group were reviewed.

Data from the two groups were collected after the individuals completed the questionnaires. For both groups, physical examinations were conducted and recorded. From the patients in both groups, 5ml of blood was taken for clinical laboratory tests (lipid profile, fasting blood glucose, postprandial blood glucose, HbA1c, and 25(OH)D level).

Cholecalciferol supplements were administered to patients in the vitamin D group six times per recommended dose schedule. The hospital would call patients once a month to remind them to take their medication. Patients in the non-vitamin D group underwent follow-up through telephone or hospital visit.

Subject is due for Visit 3 90 days from now. For both groups, midterm analyses were conducted.

Visit 3 (At 3 months)

Patients in the vitamin D group had their subject diaries for dose compliance assessed at the final session. Following that, concurrent drugs from the vitamin D group were evaluated, and additional medications from the non-vitamin D group were reviewed.

Data from the two groups were collected after the individuals completed the questionnaires. For both groups, physical examinations were conducted and recorded. From the patients in both groups, 5ml of blood was taken for clinical laboratory tests (lipid profile, fasting blood glucose, postprandial blood glucose, HbA1c, and 25(OH)D level).

Comparative t tests were used in the final analysis for both groups utilising statistical software.

IV. RESULTS AND DISCUSSION

2. RESULTS

2.1.A total of one twenty-four individuals were recruited for the research based on inclusion and exclusion criteria out of a total of 183 patients who had been evaluated for eligibility up until February 2023. Two equal subject groups are split into two groups using the block randomization approach. Cholecalciferol supplementation was given to 62 participants, whereas it was not given to the remaining 62 patients.

6.1. Basic demographic information about the vitamin D group and the non-vitamin D group

i. Gender

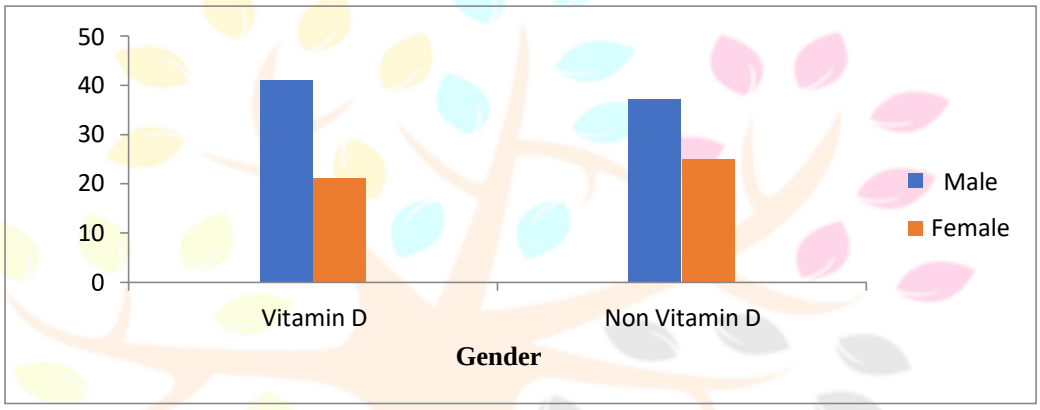

FIGURE 6.1 Gender distribution of patients in vitamin D and non-vitamin D group

Out of 124 participants in the research who were of Gujarati descent and lived in Ahmedabad, 41 were men and 21 were women in the vitamin D group, while 37 were men and 25 were women in the non-vitamin D group. (Figure 6.1).

Age Range

The mean age of over all subjects enrolled in the study was 56.08± 11.3[28-74]years.

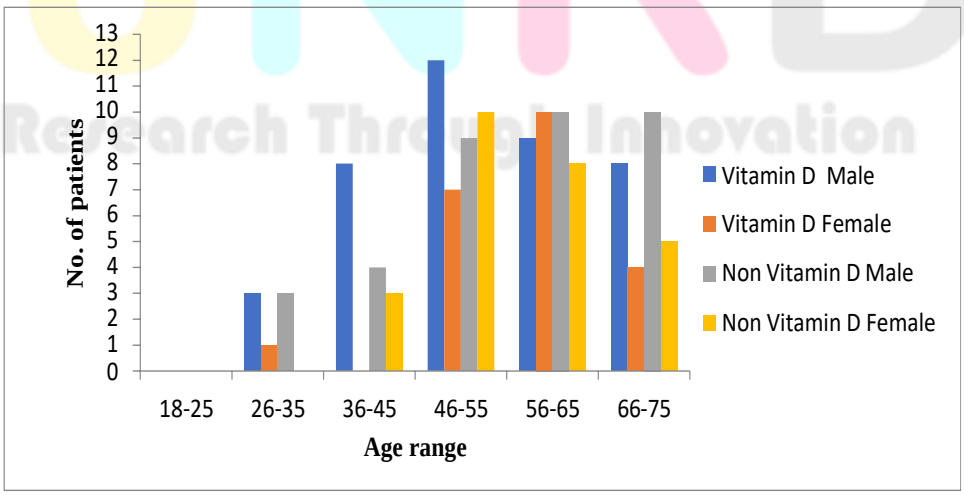

Figure 6.2: Age distribution of subjects

TABLE 6.1 Age distribution of patients in non-vitamin D and vitamin D group		
	Non-Vitamin D	**Vitamin D**
Mean Age (Male) (years)	57.4	54.34
Mean Age (Female) (years)	56.12	57
Overall mean age (years)	56.88	55.29
Age Range (Male) (years)	28-74	27-74
Age Range (Female) (years)	41-71	33-72
Overall Age range (years)	28-74	27-74

Table 6.1 shows the age ranges of both groups. Cardiometabolic diseases most often affected people between the ages of 46 and 65. (Figure 6.2). Table 6.1 shows that the average age range in the vitamin D group was 55.29 years, compared to 56.88 years in the non-vitamin D group.

Baseline Characteristics of Vitamin D and non- Vitamin D group

i. Body Mass Index (BMI):

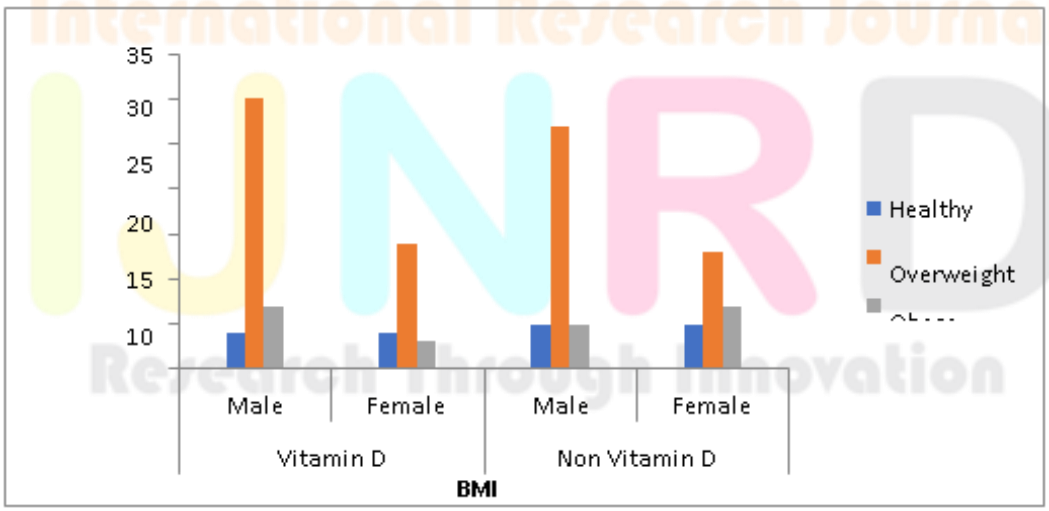

FIGURE 6.3 BMI characteristics of patients in vitamin D and non-vitamin D group

According to the BMI categorization, the healthy category is defined as (18.5-24.9) kg/m2, the overweight category as (25-29.9) kg/m2, and the obese group as >30 kg/m2. In terms of classifications based on BMI index at baseline, the majority of enrolled patients (84) were identified as being overweight. 44 patients (30 men and 14 women) in the vitamin D group and 40 patients (27 men and 13 women) in the non-vitamin D group fell into the overweight category (Figure 6.3).

Systolic Blood Pressure (SBP)

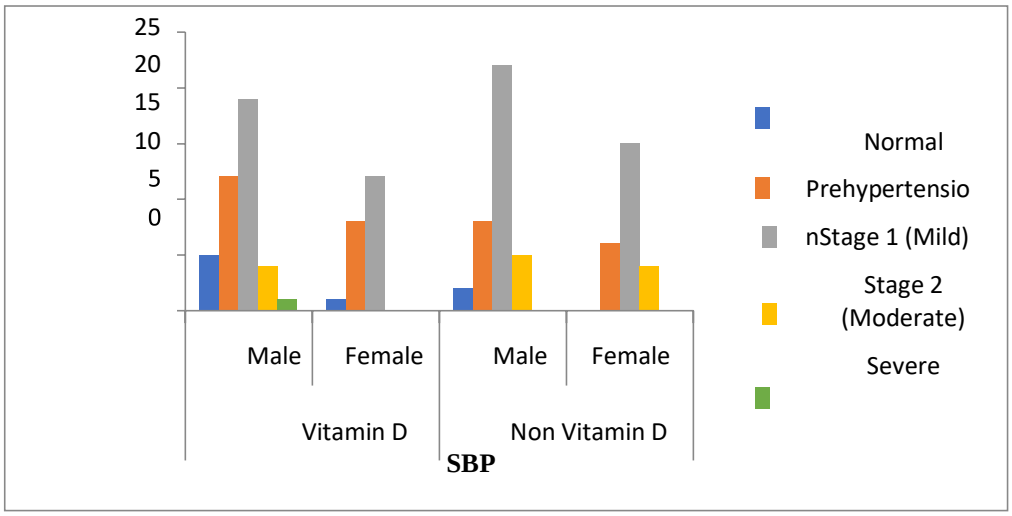

FIGURE 6.4 SBP characteristics of patients in vitamin D and non vitamin D group

According to American Heart Association (AHA) guidelines, blood pressure levels between 130 and 139 mmHg are considered normal, between 140 and 159 mmHg are considered mildly hypertensive, between 160 and 179 mmHg are considered moderately hypertensive, and between 180 and mmHg are considered severely hypertensive. At baseline, the majority of the included patients (68) to (34) were in the moderate hypertension stage. 37 patients (22 males and 15 females) in the non-vitamin D group and 31 (19 males and 12 females) patients fit into the moderate hypertension category (Figure 6.4).

Diastolic Blood Pressure(DBP):

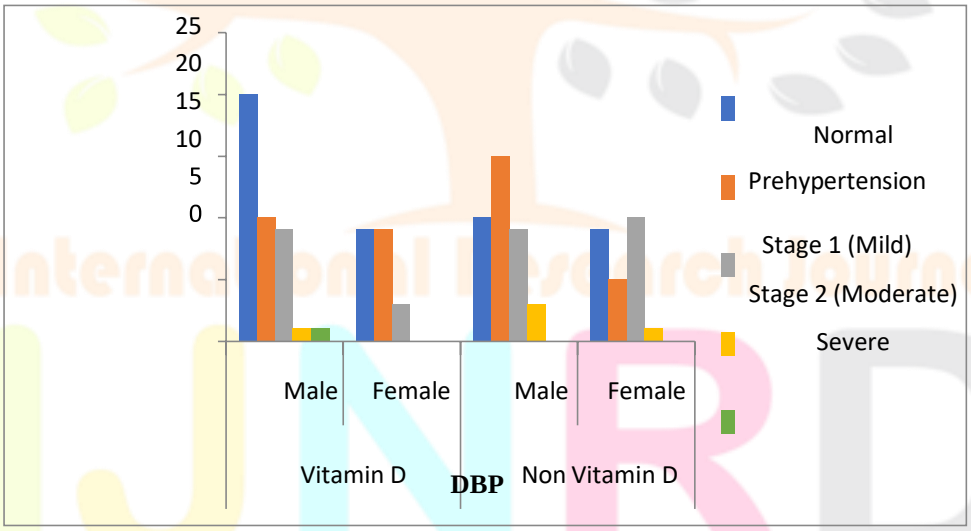

FIGURE 6.5 DBP characteristics of patients in vitamin D and non-vitamin D group

According to American Heart Association (AHA) guidelines, a blood pressure reading of less than 85 mm Hg is considered normal, more than 80 mm Hg is considered to be prehypertension, less than 90 mm Hg is considered to be mild hypertension, more than 100 mm Hg is considered to be moderate hypertension, and more than 110 mm Hg is considered to be severe hypertension [6.5]. At enrollment, the majority of the patients were in the normal (48) to prehypertensive stage (39). Prehypertensive stage is reached by 19 patients (10 men and 9 women) in the vitamin D group and by 20 patients (15 men and 5 women) in the non-vitamin D group (Figure 6.5).

Total Cholesterol (TC):

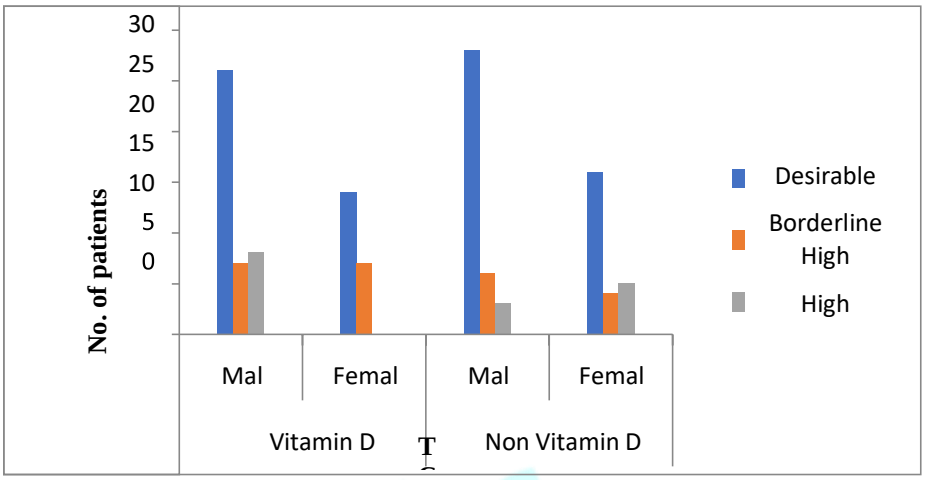

FIGURE 6.6 TC characteristics of patients in vitamin D and non-vitamin D group

A total cholesterol level of 200 mg/dl or less is classified as being in the desired range, 200 mg/dl to 239 mg/dl is classified as borderline high, and 240 mg/dl or above is classified as being in the high cholesterol group. At baseline, the majority of the recruited patients (84) are within the normal range. 40 patients (26 men and 14 women) in the vitamin D group and 44 patients (28 men and 16 women) in the non-vitamin D group had cholesterol levels that are within the ideal range (Figure 6.6).

Fasting Blood Glucose (FBG)

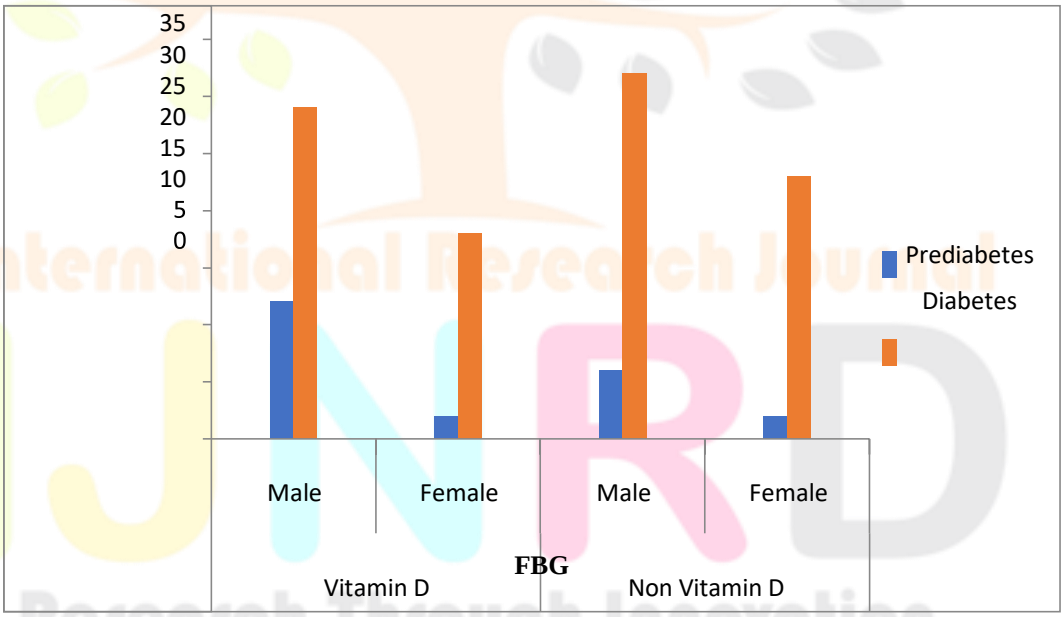

FIGURE 6.7: FBG characteristics of patients in vitamin D and non-vitamin D group

According to the American Diabetes Association (ADA), patients with FBGs between 110 and 125 mg/dl are classified as prediabetic, while those with FBGs between 126 and more are classified as diabetic. Diabetes was present in 102 out of the enrolled individuals at enrollment. In the vitamin D group, 47 people (29 men and 18 women) have diabetes, compared to 55 people (32 men and 23 women) in the non-vitamin D group (Figure 6.7).

Glycated Haemoglobin (HbA1c):

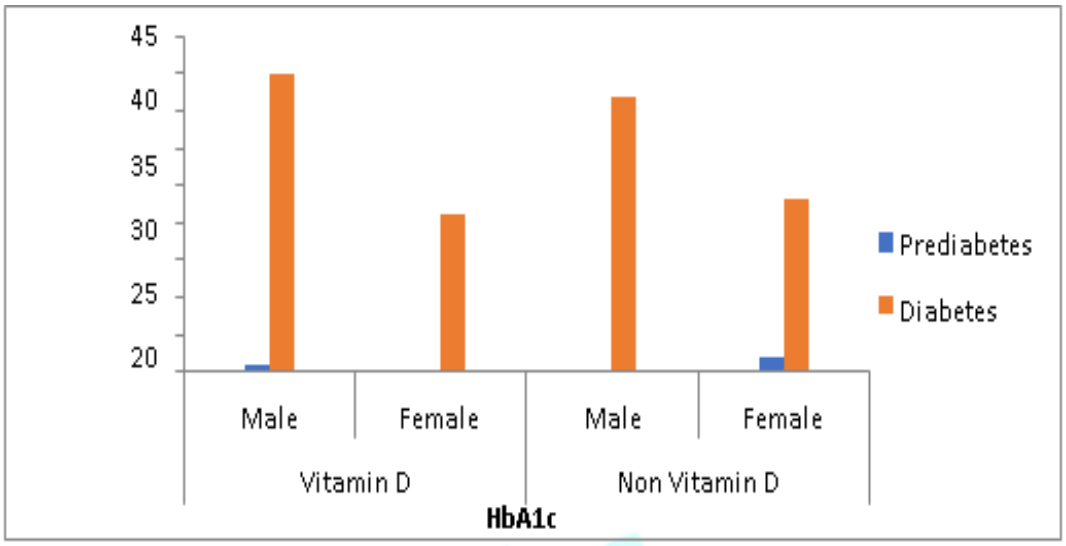

FIGURE 6.8 HbA1c characteristics of patients in vitamin D and non-vitamin D group

According to the American Diabetes Association's (ADA) recommendations, HbA1c levels between (5.7-6.5%) and >6.5% are considered to be prediabetes and diabetes, respectively. At baseline, diabetes affects 121 out of the enrolled individuals. Diabetes affects 61 individuals (40 men and 21 women) in the vitamin D group and 60 patients (37 men and 23 women) in the non-vitamin D group (Figure 6.8)

Vitamin D level {25(OH)D}:

TABLE 6.2 Range of vitamin D level in enrolled patients

	Vitamin D[Range]	Non-Vitamin D[Range]
Male	(4.3-10.4) ng/ml	(5.1-11.2) ng/ml
Female	(5-11.7) ng/ml	(4.2-11.9) ng/ml

At enrollment, the baseline 25(OH)D level for all individuals was less than 12ng/ml. Table 6.2 displays the range of baseline vitamin D levels among the patients that were enrolled.

Effect of vitamin D supplementation in patients with metabolic disorders at 0 Month and 3 Month for non-vitamin D and vitamin D group

a. Body Mass Index (BMI):

TABLE 6.3 Effect of vitamin D supplementation on BMI in non-vitamin D and vitamin D group				
	Non-Vitamin D group (n=62)		**Vitamin D group (n=62**	
Month	0	3	0	3
BMI (kg/m2)	28.09±4.27	27.95±4.25 @	27.7±3.63	27.46±3.4α
α – Within the group difference (0v1.5) (p<0.05 was considered as statistical significant) @ – Within the group difference (0v3)				

According to Table 6.3, the non-vitamin D group saw a substantial decline in BMI at months 0 and 3, whereas the vitamin D group experienced significant declines in BMI at months 0 and 1.5 as well as at months 0 and 3. However, at 1 and a half months and three months, there were no discernible changes between the groups (Non-Vitamin D vs. Vitamin D).

Systolic Blood Pressure

TABLE 6.4 Effect of vitamin D supplementation on SBP in non-vitamin D and vitamin D group						
	Non-Vitamin D group (n=62)			**Vitamin D group (n=62)**		
Month	**0**	**1.5**	**3**	**0**	**1.5**	**3**
SBP (mmHg)	143±11.2	140±10.3 α	136.8±9.67 β@	139±15.9	**134±9.41α #**	**131.9±8.09@ ***
α-Within the group difference (0v1.5) β – Within the group difference (1.5v3) **(p<0.05 was considered as statistical significant)** #-Between the group difference(1.5v1.5) @ – Within the group difference (0v3) *- Between the group difference (3v3)						

As shown in Table 6.4 , within the group analysis in non-vitamin D group showed significant reduction in SBP at (0 v 1.5) months, (1.5 v 3) months and (0 v 3) months whereas within the group analysis in vitamin D group showed significant reduction in SBP at (0 v 1.5) months and at (0 v 3) months. However, the study of the groups (Non-Vitamin D vs. Vitamin D) revealed a substantial decrease in SBP at 1.5 and 3 months.

Diastolic Blood Pressure

TABLE 6.5 Effect of vitamin D supplementation on DBP in non-vitamin D and vitamin D group						
	Non-Vitamin D group (n=62)			**Vitamin D group (n=62)**		
Month	**0**	**1.5**	**3**	**0**	**1.5**	**3**
DBP (mmHg)	85.7±7.01	81.8±6.02 $^{\alpha}$	77.81±7.34$^{\beta}$ @	83.4±7.4	79.9±5.97 α	76.32±6.40$^{\beta}$ @
α-Within the group difference (0v1.5) β – Within the group difference (1.5v3) (**p<0.05 was considered as statistical significant)** @ – Within the group difference (0v3)						

According to Table 6.5, there was a substantial decrease in DBP at 0 v 1.5 months, (1.5 v 3) months, and 0 v 0 months in both the vitamin D and non-vitamin D groups. However, an examination of DBP at 1.5 and 3 months across the groups (Non-Vitamin D vs. Vitamin D) did not reveal any appreciable differences.

Total Cholesterol (TC):

TABLE 6.6: Effect of vitamin D supplementation on TC in non-vitamin D and vitamin D group						
	Non-Vitamin D group (n=62)			**Vitamin D group (n=62)**		
Month	**0**	**1.5**	**3**	**0**	**1.5**	**3**
TC (mg/dl)	190±37.2	187.5±37.44	181.8±33.38$^{\beta}$ @	193±40.2	189.6±40.78	180.7±32.5$^{\beta@}$
β – Within the group difference (0v1.5) (**p<0.05 was considered as statistical significant)** @ – Within the group difference (0v3)						

As can be seen in Table 6.5, both the vitamin D group and the non-vitamin D group saw a substantial decrease in DBP at the three-month, six-month, and zero-month time points. At 1.5 and 3 months, however, there was no discernible change in DBP between the groups (Non-Vitamin D vs. Vitamin D).

Fasting Blood Glucose:

TABLE 6.7 Effect of vitamin D supplementation on FBG in non-vitamin D and vitamin D group						
	Non-Vitamin D group (n=62)			**Vitamin D group (n=62)**		
Month	**0**	**1.5**	**3**	**0**	**1.5**	**3**
FBG (mg/dl)	166±51.1	159±44.9	146.4±42.28$^{\beta@}$	172±58.3	145±40.9$^{\alpha}$	**124.3±33.58$^{\beta@*}$**
α – Within the group difference (0v1.5) β – Within the group difference (1.5v3) **(p<0.05 was considered as statistical significant)** *-Between the group difference (3v3) @ – Within the group difference (0v3)						

According to Table 6.7, the non-vitamin D group saw a significant decline in FBG at (1.5 v 3) months and at (0 v 3) months, whereas the vitamin D group experienced significant declines at (0 v 3) months, (1.5 v 3) months, and at (0 v 3) months. However, the FBG after 3 months significantly decreased according to the between-group study (Non-Vitamin D vs. Vitamin D).

Glycated Haemoglobin (HbA1c)

TABLE 6.8 Effect of vitamin D supplementation on HbA1c in non-vitamin D and vitamin D group						
	Non-Vitamin D group (n=62)			**Vitamin D group (n=62)**		
Month	**0**	**1.5**	**3**	**0**	**1.5**	**3**
HbA1c (mg/dl)	8.19±1.68	8.15±1.45	7.69±1.19$^{\beta@}$	8.68±1.91	7.77±1.37$^{\alpha}$	**7.05±1.08$^{\beta@*}$**
α – Within the group difference (0v1.5) β – Within the group difference (1.5v3) **(p<0.05 was considered as statistical significant)** *-Between the group difference (3v3) @ – Within the group difference (0v3)						

According to Table 6.8, the non-vitamin D group saw a significant decline in HbA1c at (1.5 v 3) months and at (0 v 3) months, whereas the vitamin D group experienced significant declines at (0 v 3) months, (1.5 v 3) months, and at (0 v 3) months. However, a comparison of the two groups (Non-Vitamin D vs. Vitamin D) revealed a substantial decline in HbA1c after three months.

25(OH)D level

TABLE 6.9 Effect of vitamin D supplementation on 25(OH)D level in non-vitamin D and vitamin Dgroup				
	Non-Vitamin D group (n=62)		**Vitamin D group (n=62)**	
Month	**0**	**3**	**0**	**3**
25(OH)D (ng/ml)	8.44±2	9±2.27	8.05±1.95	**30.8±10.9** @*
(p<0.05 was considered as statistical significant) @ – Within the group difference (0v3) *-Between the group difference (3v3)				

As can be seen in Table 6.9, the non-vitamin D group exhibited no significant differences in 25(OH)D levels within the group, but the vitamin D group showed substantial reductions in 25(OH)D levels at 0 and 3 months, as well as between the groups (Non-Vitamin D vs. Vitamin D), at the same time.

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