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# IS THERE A LINK BETWEEN VITAMIN D DEFICIENCY AND INSULIN RESISTANCE AMONG NEWLY DIAGNOSED TYPE 2 DIABETES PATIENTS? A STUDY DONE IN SUDAN

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**ABSTRACT:**

**BACKGROUNDS AND AIMS:** Diabetes mellitus remains one of the most challenging diseases, with increasing morbidity and mortality, despite excessive research. The objective of this study is to establish the association between vitamin D concentrations and insulin resistance in individuals recently diagnosed with diabetes (type 2).

**METHODS:** In this descriptive study (cross-sectional study), 65 randomly chosen non-diabetic controls and 115 recently diagnosed diabetic participants were enrolled. During the referral for diabetes mellitus diagnosis, fasting blood samples were collected from both patients and control subjects. Plasma was used to measure the concentrations of vitamin D, as well as the levels of insulin and plasma glucose during fasting. The homeostasis model assessment-estimated insulin resistance (HOMA-IR) was calculated using fasting insulin and glucose to assess insulin resistance. Each participant's weight, length, and age were recorded; these measurements were used to group the participants according to age and body mass index (BMI). Hierarchical regression analysis was performed to determine the impact of gender, age, BMI, and vitamin D on fasting insulin level and insulin resistance.

**RESULTS:** The mean vitamin D concentration was significantly lower in newly diagnosed diabetics compared to controls ($P < 0.001$). In the study group, Vitamin D levels averaged 10.7 ng/ml with a standard deviation of 7.9, while the control group had an average of 56.5 ng/ml with a standard deviation of 29.0. In contrast, the study group exhibited a significantly higher mean plasma insulin level compared to the control group ($P < 0.001$). Insulin level was ($19.7 \pm 6.2$ m U/L) and ($9.5 \pm 2.4$ m U/L) among diabetic and control groups respectively. Hierarchical regression analysis confirmed a significant negative correlation between the amount of vitamin D and insulin during fasting and insulin resistance ($P= 0.0001$).

**CONCLUSION:** Vitamin D deficiency is strongly related to hyperglycemia, hyperinsulinemia, and insulin resistance in newly diagnosed diabetic patients (type 2).

**KEYWORDS:** Vitamin D, Diabetes Mellitus Type 2, Insulin Resistance, HOMA-IR.

**INTRODUCTION:**

Vitamin D deficiency was implicated as a risk factor for type II diabetes mellitus based on numerous data from studies including both humans and animals. The contribution of vitamin D deficit to the development of type II diabetes mellitus could be through disrupting the activity of the β-cells, increasing insulin resistance, and causing chronic inflammatory diseases [1]. On the other hand, studies including sun exposure and vitamin D intake supported the potential effect of vitamin D in reducing the risk of type 2 diabetes. Lindqvist et al found that greater sun exposure is correlated with a lower risk of developing type 2 diabetes and better parameters of glycemic control namely HbA1c [2]. Similar findings were observed in other studies that examined the effect

of vitamin D intake and the chances of developing type 2 diabetes [3, 4]. Despite inconsistency in their findings, many prospective, cross-sectional studies and meta-analyses reported a negative association between vitamin D plasma concentrations and glycemic control, insulin resistance, type 2 diabetes, and metabolic syndrome [5-8]. On the other hand, randomized controlled clinical trials on normal populations, and populations at risk or with frank type 2 diabetes failed to prove the hypothesis on which these studies were built (deficiency of vitamin D is a risk or causal factor for insulin resistance or type 2 diabetes) [9-16] except few of them [17-19]. In our study, we investigated the association between vitamin D and many parameters for diagnosis of type two diabetes mellitus including hyperglycemia, hyperinsulinemia, and insulin resistance to validate its role in the pathogenesis of type 2 diabetes mellitus.

## MATERIAL AND METHODS:

In this hospital-based cross-sectional study, one hundred fifteen subjects who were diagnosed for the first time with type II diabetes mellitus participated in the study. Ethical approval was obtained from Shendi University. Informed consent was signed by each participant after clarifying the purpose of the study and all steps a participant would be involved in. Participants' age range was 15 – 93 years. Diagnosis of diabetes mellitus in all participants was confirmed through measurement of fasting plasma glucose levels (FPG ≥ 126mg/dl). Sixty-five healthy adults were randomly recruited as a control group. Participants with acute and chronic infections and vitamin D supplementation were excluded from the study.

5 milliliters of venous blood were collected using a disposable sterile syringe from patients (referred for diabetes mellitus diagnosis) and controls following a minimum eight-hour fasting period. The blood was transferred into test tubes containing fluoride oxalate. Then these samples were centrifuged within a maximum of two hours after collection, and the plasma was isolated and preserved at a temperature of -20°C. Stored plasma samples were used to assess plasma vitamin D and insulin concentrations using enzyme-linked immunosorbent assay (ELISA), besides fasting plasma glucose by Colorimetric, enzymatic method with glucose oxidase using an automated analyzer. ELISA instruments were supplied by Biotek Instruments (USA), while ELISA kits were supplied by Sunlong Biotech (China).

For all participants, weight and height were measured using standard scales and they were used to calculate the BMI, accordingly, the patients and controls were subdivided into four subgroups underweight, normal weight, overweight, and obese group according to BMI criteria created and revised by WHO (1995, 2000 and 2004). The effects of age variation were eliminated by stratifying both the patient and controls into age groups.

### Statistical analysis:

The study's results were analyzed using the Statistical Package for the Social Sciences (SPSS) software (V.21) 64-bit for Windows 8. Independent t-test, one-way and two-way analysis of variance (ANOVA), and hierarchical (sequential) regression were used. To fulfill the assumptions

of sequential regression data transformation was carried out; where the dependent variable (HOMA-IR) was transformed into square root form, while the independent continuous variables (age, BMI, and vitamin D levels) were transformed into a log form. The study was demarcated as statistically significant at a P-value less than 0.05.

**Ethical consideration:**

All procedures complied with the ethical standards set by the pertinent institutional and national committee for human experimentation; the Helsinki Declaration of 1975, as revised in Brazil in 2013.

**RESULTS:**

An entire group of 180 participants were selected for this study, comprising 115 diabetics (63.9%) and 65 controls (36.1%). Table 1 presents several features of the diabetes and control groups.

The male-to-female ratio in the diabetes cohort was roughly 1:2, whereas in the control cohort it was around 1:1. The average ages ± standard deviation in years for males and females within the diabetes cohort comprised 65 ± 13.9 as well as 58.7 ± 15.5, respectively ($P < 0.05$), whereas the corresponding values in the control group were 39.2 ± 16.4 and 43.4 ± 15.7 ($P > 0.05$). There were also notable disparities in the average ages of diabetic males and girls when compared to their control counterparts ($P < 0.0001$) over both groups.

**Table 1: Comparison of mean age, mean weight, mean height, mean BMI, and gender distribution between diabetics and controls.**

| | Diabetics | | | Controls | | |
|---|---|---|---|---|---|---|
| | **Male batch** | **Female batch** | **Combine** | **Male batch** | **Female batch** | **Combine** |
| **Numerals** | 34 (29.6%) | 81 (70.4%) | 115 | 26 (40%) | 39 (60%) | 65 |
| **Average age (Year) ± SD** | 65 ± 13.9 | 58.7 ± 15.5 | 60.6 ± 15.2 | 39.2 ± 16.4 | 43.4 ± 15.7 | 41.7 ± 16 |
| **Average weight (Kg) ± SD** | 73.3 ± 11.9 | 75.1 ± 13.7 | 74.6 ± 13.1 | 66.5 ± 10.9 | 64.9 ± 10 | 65.5 ± 10.3 |
| **Average height (m) ± SD** | 1.7 ± 0.1 | 1.6 ± 0.1 | 1.6 ± 0.1 | 1.7 ± 0.1 | 1.6 ± 0.1 | 1.7 ± 0.1 |
| **Average BMI ($Kg/m^2$) ± SD** | 27 ± 4.2 | 28.7 ± 5 | 28.2 ± 4.9 | 23.7 ± 3.3 | 23.8 ± 2.8 | 23.8 ± 3 |

The average BMI (i.e. in kg / (height in m²) increased considerably in diabetics (28.2 ± 4.9 kg/m²) compared to controls (23.8 ± 3 kg/m²) (P < 0.001). This trend was similarly observed among diabetic females (28.7 ± 5 kg/m²) versus control females (23.8 ± 2.8 kg/m²) (P < 0.001), and diabetic males (27 ± 4.2 kg/m²) versus control males (23.7 ± 3.3 kg/m²) (P < 0.001).

Table 2 displays the levels of vitamin D. The average plasma concentration of vitamin D was much lower in the diabetes cohort. (10.7 ± 7.9 ng/ml) compared to that in the control group (56.5 ± 29.0 ng/ml) (P < 0.001). This significant decline in vitamin D persists when groups are subdivided by gender into male and female groups.

Figure 1 shows differences in vitamin D concentration among different age and BMI subgroups. The group of controls had the greatest average plasma content of vitamin D in underweight individuals. (86.5 ± 19.2). It declines progressively in the normal-weight subjects (57.5 ± 28.6) and overweight subjects (53.7 ± 28.9) to attain a minimal value in individuals with obesity (25.3 ± 13.8).

among the diabetic cohort, the greatest mean plasma levels of vitamin D were seen among underweight individuals. (12.3 ± 10.3). Other BMI subgroup levels of vitamin D were 10.9 ± 7.9, 10.5 ± 8.1, and 10.8 ± 7.9 for the normal-weight, Individuals classified as overweight and obese, respectively. The mean plasma concentration of vitamin D was considerably elevated in the control group across all four BMI categories compared to the diabetes group (P < 0.05 for underweight individuals, < 0.001 for normal weight and overweight individuals, and < 0.05 for obese individuals).

The plasma vitamin D concentrations were substantially elevated in controls vs to diabetes across all age demographics (P < 0.001). While differences in vitamin D concentration in each age subgroup within the control or diabetes groups were insignificant.

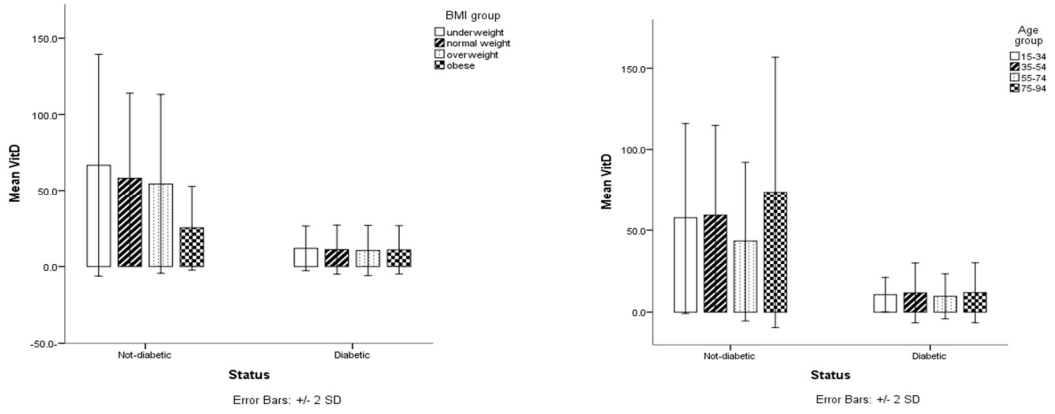


**Figure 1: Distribution of mean plasma concentrations of vitamin D (ng/ml) among control and diabetic subjects by BMI and age subgroups.**

**Table 2: Distribution of mean plasma concentrations of vitamin D (ng/ml) and insulin (mU/L) among control and Type 2 diabetes individuals across gender.**

| Gender | Variable | Status | N | Mean | SD | P value |
|---|---|---|---|---|---|---|
| Male | Vit. D | Control | 26 | 60.4 | 31.2 | 0.000 |
| | | Diabetic | 34 | 8.6 | 6.1 | |
| | Insulin | Control | 26 | 9.2 | 1.8 | 0.000 |
| | | Diabetic | 34 | 19.4 | 6.0 | |
| Female | Vit. D | Control | 39 | 53.9 | 27.5 | 0.000 |
| | | Diabetic | 81 | 11.6 | 8.4 | |
| | Insulin | Control | 39 | 9.7 | 2.7 | 0.000 |
| | | Diabetic | 81 | 19.8 | 6.3 | |

Table 2 shows the average fasting insulin concentration. The diabetic individuals had a considerably higher level. (19.7 ± 6.2 m U/L) compared to the control group (9.5 ± 2.4 m U/L) ($P < 0.001$). Dividing both groups into male and female subgroups does not affect the significant variation.

Figure 2 shows the mean fasting insulin in different BMI subgroups. BMI was used for dividing the groups into subgroups to eliminate the effect of BMI and hence adiposity on insulin resistance. Most of the participants (73.1%) in the study group were overweight or obese (37.4% and 35.7% respectively). Whereas 35.4% in the control group were overweight and only 3.1% were obese. Within the diabetic cohort, underweight participants had the lowest average blood level of insulin, and the highest was noted among the obese subgroup (the mean square root of fasting insulin was 3.79 ± 0.06 and 4.46 ± 0.72 among underweight and obese subgroups respectively). The square root of the mean fasting plasma insulin (FI-sqr) concentration in the four BMI The incidence of subgroups was much higher in the diabetes cohorts than in the respective control subgroups ($P < 0.05$ for underweight and obese individuals, and $P < 0.001$ for normal weight and overweight individuals). Plasma insulin concentrations were elevated in diabetics relative to controls across all age demographics, p-value of $< 0.001$ in the first two age groups, and $< 0.01$ in the last age group. There were insignificant differences when comparing each age subgroup within the control or diabetes groups.

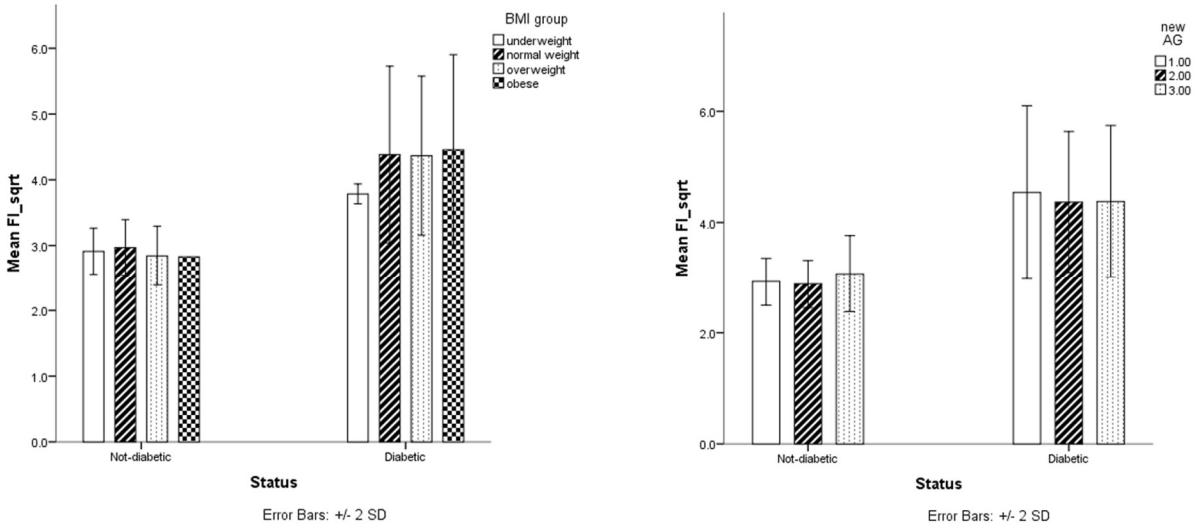


**Figure 2: Distribution of mean plasma fasting insulin square root of (m U/L) in control and diabetes populations classified through BMI and age categories.**

HOMA-IR was used to assess insulin resistance. HOMA-IR = fasting insulin (mU/L) *FBS (mg/dl)/405.

Insulin resistance (IR) was significantly higher in diabetic subjects (9.7 ± 4.9) compared to controls (1.9 ± 0.5) $P < 0.001$. When the participant was grouped according to their gender, IR was significantly higher in both diabetic males (8.8 ± 3.8) and females (10.1 ± 5.2) compared to their respective controls (1.9 ± 0.4, 1.9 ± 0.5) respectively and the P values for both were less than 0.001. Gender did not have an impact on IR in both study and control groups. When the grouping was based on BMI, IR increased progressively from the underweight toward the obese group. The respective values of IR in the underweight, normal weight, overweight and obese groups were 8.0 ± 3.7, 9.3 ± 3.9, 9.7 ± 4.9, and 10.2 ± 5.5 respectively but the differences between each group and the others were statistically insignificant ($P > 0.05$). Comparing each BMI group in diabetics with its respective one in controls led to statistically significant higher IR in diabetic groups with $P < 0.001$ in normal weight and overweight, and $P < 0.01$ in underweight except in the obese group where it was insignificant $P > 0.05$.

When the participants were clustered according to their ages, in both diabetic and control groups the differences within the same groups were insignificant. Comparing each group in diabetics to its respective one in controls led to statistically significant higher IR in diabetic groups with $P < 0.001$ in the first two groups and $P < 0.05$ in the last one.

Hierarchical (sequential) A multivariate regression analysis was used to figure out whether the addition of age, BMI and then vitamin D concentration improved the prediction of insulin resistance that is calculated as HOMA-IR over and above gender patients recently diagnosed type II diabetes. The comprehensive model incorporating gender, age, BMI, and logarithmic vitamin D

demonstrated great statistical significance (P = 0.0001), with R = 0.659, $R^2$ = 0.434, and modified $R^2$ = 0.409. (Table 3)

**Table 3: Values of R, $R^2$, and modified $R^2$ in the model estimating HOMA-IR:**

| Dependent variable | R | $R^2$ | Adjusted $R^2$ | P value |
|---|---|---|---|---|
| **IR-sqr** | 0.659 | 0.434 | 0.409 | 0.0001 |

The comprehensive model demonstrated an extremely significant inverse correlation among log vitamin D content and IR-sqr (P = 0.0001). The associations of other predictors with IR-squared were positive.
nevertheless, they were statistically insignificant. Refer to table 4.

**Table 4 Standardized (β) and unstandardized (B) coefficients for different predictors of HOMA-IR**

| Predictor | B | B | P value |
|---|---|---|---|
| Constant | 0.572 | | 0.622 |
| Gender | 0.211 | 0.100 | 0.109 |
| Age | 0.007 | 0.117 | 0.095 |
| BMI | 0.019 | 0.094 | 0.166 |
| Log vitamin D | -1.002 | -0.471 | 0.0001 |

Hierarchical regression was run to determine the prediction magnitude of fasting insulin square root (FI-sqr) by gender, age, BMI, and vitamin D in newly diagnosed type II diabetes. The overall model including gender, age, BMI, log vitamin D was statistically highly significant (P = 0.0001), with R = 0.647, $R^2$ = 0.419 and adjusted $R^2$ = 0.393. Refer to Table 5.

**Table 5: Values of R, $R^2$ and adjusted $R^2$ in the model predicting fasting insulin**

| **Dependent variable** | **R** | **$R^2$** | **Adjusted $R^2$** | **P value** |
|---|---|---|---|---|
| FI-sqr | 0.647 | 0.419 | 0.393 | 0.0001 |

The overall model showed a statistically highly significant negative correlation between log vitamin D concentration and FI-sqr (P = 0.0001). The correlations of other predictors with FI-sqr were positive, but all of them were not statistically significant as shown in the coefficient table. Refer to table 6

**Table 6: Standardized (β) along with unstandardized (B) coefficients for several predictors of fasting insulin.**

| Predictor | **B** | **B** | **P value** |
|---|---|---|---|
| Constant | 3.312 | | 0.002 |
| Gender | 0.113 | 0.062 | 0.323 |
| Age | 0.006 | 0.124 | 0.080 |
| BMI | 0.021 | 0.113 | 0.102 |

| | | | |
|---|---|---|---|
| Log vitamin D | -0.958 | -0.508 | 0.0001 |

**DISCUSSION:**

Our study revealed significant differences in plasma concentrations of fasting insulin and vitamin D between newly diagnosed diabetics and control subjects.

Our results were similar to most other studies that compared the levels of these two parameters between diabetic patients and controls [1-8, 17-19]. The debate continues on whether vitamin D deficiency is a contributing risk factor for the development of insulin resistance in diabetes Mellitus (type II ). Vitamin D deficit has been related to the development of insulin resistance in type II diabetes, which proposes that adequate levels of this nutrient could be reflected in the modulation of insulin sensitivity.

It is well known that body fat content affects plasma vitamin D concentration [21], so we classified the diabetic subjects into four subgroups by their body mass indices and compared each group with its counterpart in the control subgroups. Additionally, it is recognized that the fat content in females is higher than in males, which serves to mitigate the differences in body composition between diabetics and non-diabetics. Another factor that may have such an effect is the age factor because aging is associated with less physical activity which may lead to less sun exposure in addition to reduced skin capacity for synthesis of vitamin D, hence we stratified both diabetics and controls into three age groups and each age group of a diabetic was compared to its counterpart of controls as age was statistically greater in diabetics Upon reviewing all factors, it was determined that the average plasma concentration of Vitamin D levels were found to be significantly lower in the diabetic group compared to the control group, regardless of gender, age, and body mass index (BMI). This observation aligns with research indicating that individuals with diabetes often have vitamin D deficiencies, which can influence various health outcomes results were consistent with that of Muscogiuri et.al [22] in the correlation between body mass index and plasma vitamin D levels as we observed vitamin D concentrations decreased progressively from the underweight group towards the obese one very clearly in controls and to a lesser extent in diabetics. This is explained by the fact that excess body fat binds much of the circulating plasma form of vitamin D lowering their plasma concentration as it is a fat-soluble vitamin [22]. All diabetic BMI subgroups have significantly lower vitamin D concentrations compared to their counterpart subgroup except the obese subgroup and this could be attributed to the effect of body fat in lowering vitamin D.

On the other hand, our finding for correlation between age and vitamin D was inconsistent with that of Fulvio et.al [23] who stated that vitamin D levels decrease with advancing age, and the reason for this may be the inadequate number of participants in the first age group (15-40 years) of diabetics (only 12) and last age group (71-94 years) of controls (only two subjects). Another

reason may be the difference in latitude between Sudan and Europe where the study by Fulvio et.al was carried leading to the different degrees of U.V irradiant and the nature of housing in Sudan.

What makes our study unique is the significant negative correlation between vitamin D and insulin resistance and vitamin D and fasting insulin level. Despite this, the majority of randomized clinical trials have not confirmed that vitamin D administration can enhance insulin sensitivity or decrease the risk of type 2 diabetes mellitus. However, this may be due to the dosage and duration of vitamin D treatment. Algamdi et al. reported that a high dose of vitamin D, specifically 50,000 IU weekly, improved insulin resistance in Saudi women [23].

## CONCLUSION:

According to our findings, vitamin D deficiency is strongly correlated with insulin resistance in newly diagnosed type 2 diabetic Sudanese patients.

### Recommendations:

More clinical trials are to be performed using high-dose vitamin D to reduce insulin resistance.

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### Conflict of Interest:

The authors have disclosed that no conflicts of interest exist.

### Data Availability

The data supporting the findings of this study can be obtained from the corresponding author upon a reasonable request.

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