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# Effect of Vitamin D Supplementation in a Sample of Type 2 Diabetes Patients from Karak Governorate in Jordan

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**Abstract:** Vitamin D status of type 2 diabetes mellitus (T2DM) patients in Karak Governorate in Jordan was assessed and the relationship between vitamin D supplementation and blood glucose was found. The study recruited thirty three confirmed T2DM subjects (19 males and 14 females) with deficient or insufficient vitamin D status. They were given a supplement of 2000 IU of vitamin $D_3$ daily for 1 month. Fasting blood samples were taken before and after supplementation. Serum levels of fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), calcium (Ca), insulin, parathyroid hormone (PTH) and 25 hydroxyvitamin $D_3$ (25 (OH) $D_3$) were determined and the homeostasis model assessment-insulin resistance (HOMA-IR), homeostasis model assessment-beta secretion (HOMA-beta) and quantitative insulin sensitivity check index (QUICKI) indices were calculated. The statistical analysis of experimental data indicates that there was a significant increase ($p<0.0001$) in mean 25(OH) $D_3$ levels after one month supplementation with the vitamin (from 31.1±1.9 to 68.1±6.1 nmol/L). A significant decrease in serum insulin level (16.5±3.7 vs. 9.0±1.1 μU/mL; $p<0.0001$) was also found, together with significant improvement in functions of HOMA-IR ($p<0.0001$), HOMA-beta ($p = 0.0006$) and QUICKI ($p<0.0001$) in both sexes without any significant differences between them. This study shows that giving vitamin D supplement for one month to diabetic patients with insufficient vitamin level increases 25(OH) $D_3$ concentrations and resulted in improvements in many diabetic indices.

**Key words:** Vitamin D deficiency, type 2 diabetes, vitamin D supplementation, fasting blood glucose, glycosylated hemoglobin, HOMA-IR, HOMA-beta, QUICKI

## INTRODUCTION

Vitamin D deficiency is currently recognized as a global epidemic and has been linked to many diseases such as cardiovascular diseases and diabetes mellitus (Muscogiuri *et al*., 2012). A major cause of vitamin D deficiency is inadequate exposure to sunlight and also it depends on the activity of the enzymes responsible for its final hydroxylation in the body (Engelsen, 2010; Chun, 2012; Henry, 2011).In addition, other factors affect vitamin D status; these include genetic factors, adiposity and factors affecting the cutaneous synthesis of vitamin D such as skin pigmentation, age, season, latitude, time spent outdoors, clothing and the use of sunscreens (Mezza *et al*., 2012). Few foods naturally contain vitamin D and foods that are fortified with vitamin D are often not sufficient to provide adequate intake of the vitamin (Zhang and Naughton, 2010). In Jordan, although considered a sunny country all over the year except in winter, several studies revealed a high prevalence of low serum 25-hydroxyvitamin $D_3$ (25 (OH) $D_3$) <30 ng/mL both in females and males with different ages (Mallah *et al*., 2011; Jazar *et al*., 2011; Mishal, 2001; Gharaibeh and Stoecker, 2009; Batieha *et al*., 2011).

T2DM is a serious metabolic disorder that has become increasingly prevalent all over the world (Moreira and Hamadeh, 2010). It is caused by insulin resistance (IR) and pancreatic islet insufficiency (Patel *et al*., 2010). Good glycemic control remains important in diabetes management (Del Prato *et al*., 2010). It was shown in several studies that vitamin D deficiency may play a role in the pathogenesis of T2DM by increasing insulin resistance and decreasing insulin secretion in human and animal models (Meerza *et al*., 2010; Pittas and Dawson-Hughes, 2010). According to the Jordanian Ministry of Health statistics (MOH), about 16% of Jordanians over 18 years of age (approximately 300 000 persons), were found to have diabetes (fasting blood glucose (FBG) = 126 mg/dL) and about 24%, or 450 000 persons are prediabetic (FBG 100-125 mg/dL) (Ministry of Health, 2010). Diabetes Mellitus is also a common problem in the southern part of Jordan including Karak Governorate with a population of approximately 249000 (Department of Statistics, 2012). In the current study, we aimed to investigate the impact of vitamin D supplementation on blood glucose levels and glycemic indices in T2DM patients with inadequate vitamin D levels.

## MATERIALS AND METHODS

**Site and duration of the study:** This experimental study was conducted on patients (30-60 years) visiting the outpatient endocrinology clinic of Karak Governmental

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Hospital in southern Jordan, during the months from October 2011 to January 2012. The study was approved by the Research Ethics Committee of the Hospital and the Graduate Studies Committee of the University of Jordan. All subjects were requested to provide written informed consents prior to the study.

**Subjects:** Thirty-three subjects (19 males and 14 females) included in the study were all confirmed as T2DM patients and having low serum vitamin D (below 50 nmol/L). Subjects selected were free from other medical problems and were not taking medications that could influence vitamin D status such as anticonvulsant drugs, diuretics, mineral oils laxatives, or suffering from diseases such as intestinal malabsorption, steatorrhea, celiac disease, inflammatory bowel disease, pancreatic insufficiency, hepatic disorders and chronic renal failure. Also subjects receiving supplements of vitamin D before the study were excluded as well as those required by the physician to adjust the dose of hypoglycemic agents they receive. Full medical history for the volunteers was taken by the hospital physician.

Dietary information of vitamin D intake was obtained using a food frequency questionnaire (Lee and Nieman, 2010). Subjects were given 2000 IU vitamin $D_3$ (Biodal, Al-Hayat Pharma, Jordan) to be taken daily with dinner for a period of one month. They were instructed to keep their dietary habits unchanged and not to change any of their medications.

**Anthropometry:** Height and weight of subjects were measured at the beginning of the study and body mass index (BMI) was calculated using the following equation:

$$BMI = Weight\ (kg)/Height\ (m)^2$$

where, (Lee and Nieman, 2010).

**Biochemical parameters and indices:** Fasting blood samples were collected before and after supplementation for the determination of six different biochemical tests: fasting plasma glucose (FPG), serum calcium (Ca), glycosylated hemoglobin (HbA1c), serum insulin, parathyroid hormone (PTH) and serum vitamin D. The first three tests were determined using routine laboratory procedures (COBAS INTEGRA/400, Roche, USA). Serum insulin level was quantified using chemi luminescent microparticle immunoassay (CMIA) (ARCHITECT, Abbott Laboratories, USA). Parathyroid hormone (PTH) and serum vitamin D (25 (OH) D) were measured using enzyme-linked immunosorbent assay (ADALTIS/Italy and ADALTIS/Spain, respectively). The homeostasis model assessment-insulin resistance (HOMA-IR) was calculated as:

1: FBG (mmol/L) x serum insulin level (µU/mL)/22.5. The homeostasis model assessment-beta secretion (HOMA-beta) (%) was calculated as:
2: 20 x serum insulin level (µU/mL)]/[FBG (mg/dL)-3.5 and the quantitative insulin sensitivity check index (QUICKI) was calculated as:
3: 1/[log serum insulin level (µU/mL) + log FBG (mg/dL)]. Vitamin D deficiency and insufficiency levels were defined as serum 25 (OH) D level <30 nmol/L and between 30-50 nmol/L, respectively (Institute of Medicine, 2010)

**Statistical analysis:** Statistical analysis was performed using Statistical Analysis System (SAS), version 9 at the University of Jordan. The results of each variable studied were subjected to analysis of Variance (ANOVA) for continuous variables, followed by Least Significant Difference (LSD). The association between serum vitamin D and other parameters was assessed using Pearson Correlation Coefficient. Results were expressed as means±standard error of means (SEM) and frequency distribution. $p<0.05$ was considered significant.

## RESULTS

This study included 33 diabetic subjects (19 males and 14 females), their general characteristics are shown in Table 1. Mean age was 48.4±1.2 year, BMI was 29.0±0.7 $Kg/m^2$ and vitamin D daily intake was found to be 1.5±0.2 µg. Table 2 shows the biochemical characteristics of the subjects, where there was a significant increase in mean 25(OH) $D_3$ level after supplementation with vitamin D (31.1±1.9 nmol/L before vs. 68.1±6.1 nmol/L after; $p<0.0001$). Also there was a significant decrease in serum Ca (68.3±4.3 mg/dL vs. 65.0±8.2 mg/dL; $p = 0.0004$) as well as significant decrease in serum insulin level (16.5±3.7 vs. 9.0±1.1 µU/mL; $p<0.0001$). In addition, there was a significant improvement in functions of HOMA-IR ($p<0.0001$), HOMA-beta ($p = 0.0006$) and QUICKI ($p<0.0001$). In both sexes, supplementation resulted in significant ($p<0.05$) improvements in serum vitamin D, insulin and HOMA-IR as shown in Table 3. The correlation coefficients (r)

Table 1: Baseline characteristics and biochemical parameters and indices of the diabetic study groups*

| Variable | Total n = 33 | Males n = 19 | Females n = 14 | p-value |
|---|---|---|---|---|
| Age (years) | 48.4±1.2 | 50.2±1.6 | 46.1±1.5 | 0.4 |
| Body mass index ($kg/m^2$) | 29.0±0.7 | 29.3±1.2 | 28.7±0.8 | 0.07 |
| T2DM duration (years) | 2.6±0.5 | 3.0±0.7 | 2.2±0.8 | 0.9 |
| Vitamin D intake (µg/day) | 1.5±.0.2 | 1.5±0.2 | 1.6±0.3 | 0.2 |

*Mean±SEM, p-value significant at <0.05 between males and females

Table 2: General characteristics and biochemical parameters and indices of the study group*

| | ---------- Total n = 33 ---------- | | |
|---|---|---|---|
| Variable | Before | After | p-value |
| Fasting blood glucose (mg/dL) | 173.7±12.9 | 140.1±9.9 | 0.1 |
| % <110 mg/dL | 6.1 | 27.3 | |
| Glycosylated hemoglobin (%) | 7.9±0.3 | 7.8±0.4 | 0.4 |
| % <6.5% | 24.2 | 42.4 | |
| Serum insulin (µU/mL) | 16.5±3.7 | 9.0±1.1 | <0.0001 |
| % <11 µU/mL | 54.5 | 72.7 | |
| HOMA-IR | 7.4±2.1 | 3.1±0.5 | <0.0001 |
| % <2.6 | 30.3 | 57.6 | |
| HOMA-beta (%) | 2.1±0.4 | 1.5±0.2 | 0.0006 |
| % <2.6 | 75.8 | 87.9 | |
| QUICKI | 0.31±0.01 | 0.35±0.02 | <0.0001 |
| % >0.33 | 24.2 | 39.4 | |
| Parathyroid hormone (ρg/mL) | 68.3±4.3 | 65.0±8.2 | 0.0004 |
| % <55 ρg/mL | 33.3 | 42.4 | |
| Serum calcium (mg/dL) | 9.5±0.1 | 9.0±0.1 | 0.05 |
| % >8.5 mg/dL | 0.0 | 0.0 | |
| Serum vitamin D (nmol/L) | 31.1±1.9 | 68.1±6.0 | <0.0001 |
| % >50 nmol/ L | 0.0 | 57.6 | |

HOMA-IR: Homeostasis model assessment-insulin resistance; HOMA-beta: Homeostasis model assessment-beta secretion; QUICKI: Quantitative insulin sensitivity check index. *Mean±SEM, p-value significant at <0.05

between serum vitamin D and the studied biochemical variables are shown in Table 4. A significant positive correlation was found between vitamin D and HOMA-IR for the whole sample and for males and females; while a significant negative correlation was found between vitamin D and serum insulin and PTH for the whole sample and for both genders. Also a significant positive correlation was found between vitamin D and HOMA-beta and QUICKI in females only.

## DISCUSSION

The study was conducted in Karak Governorate located in the southern region of Jordan. The findings of this study indicated that serum vitamin D was low in most of the study subjects. The deficiency of vitamin D was more prevalent in females than in males. These results were similar to those obtained from different studies conducted in various parts of Jordan (Mallah *et al*., 2011; Jazar *et al*., 2011; Batieha *et al*., 2011). Age is an important factor in the photo production of previtamin $D_3$; there is an inverse relationship between the concentrations of previtamin $D_3$ in the epidermis and age (Norman, 1998). The mean age of the sample in the present study was 48.4±1.2 years. Also the vitamin D intake from its rich sources was found to be low for the whole study subjects (1.5±0.2 µg/day). In Karak Governorate rural lifestyle predominates and people depend mainly on locally produced foods; they generally consume home-made bread prepared from whole flour rather than purchasing vitamin D fortified bread. They also consume locally produced unfortified milk and dairy products.

Both females and males were in the overweight and obese categories (BMI $\geq$25 Kg/m$^2$). This result is consistent with the results of many studies on vitamin D status suggesting that the larger body fat compartments may reduce the bioavailability of vitamin D from cutaneous and dietary sources because of its deposition in body fat compartments (Al-Daghri *et al*., 2012; Forrest and Stuhldreher, 2011).

HOMA and QUICKI are simple, indirect methods for the detection of insulin resistance. HOMA is considered a valid method to assess peripheral insulin sensitivity in epidemiologic studies (Yokoyama *et al*., 2004; Mizrahi *et al*., 2010). The values of HOMA-IR obtained before and after supplementation of the vitamin in this study were above the normal values (the normal value is $\leq$2.6). A similar result was found for HOMA-beta. Furthermore, the calculated QUICKI value was higher than normal ($\geq$0.33%) with significant difference just in males. These results indicate the presence of insulin resistance in male subjects, which might be related to the overweight and high BMI (Ascaso *et al*., 2003). QUICKI index showed no significant difference in females before and after supplementation of the vitamin even though the majority of them had values $\geq$0.33. HOMA and QUICKI are based on fasting glucose and insulin levels and primarily reflect hepatic insulin sensitivity (i.e., the ability of insulin to suppress hepatic glucose production) which is related to diabetes occurrence (Chen *et al*., 2007). Hypovitaminosis D is known to cause a compensatory increase in the secretion of PTH to increase Ca resorption from the skeleton and reabsorption in the kidneys and inhibits insulin synthesis and secretion from beta-cells (Autier *et al*., 2012; Talaei *et al*., 2013).

In this study vitamin D supplementation was significantly associated with improvement in serum insulin, HOMA-IR, HOMA-beta secretion, QUICKI index and serum vitamin levels with significant differences ($p<0.05$). Also vitamin D supplementation tended to improve the levels of FBG and HbA1c although not significantly (Table 2). The Food and Nutrition Board and the European Commission Scientific Committee on Food have selected 50 µg (2000 IU) vitamin $D_3$ as a safe tolerable upper daily intake level (Aloia *et al*., 2008). This was the amount of vitamin D supplied to subjects of the present study. However, this present study was limited in time of vitamin D supplementation; longer time of supplementation is needed showing the vitamin D effect. It is well-established that there is a relationship between insufficient vitamin D status and T2DM (Stivelman and Retnakaran, 2012). Treatment with both vitamin $D_2$ and $D_3$ improved 25(OH) D concentrations in diabetic patients even not to sufficient levels (Alam *et al*., 2013). However, the number of studies in the literature is limited. The results observed in some of those studies have been contradictory (although no study has shown worsening or prevention of the emergence of the disease). Although more studies are needed to confirm the role of vitamin D in the treatment of T2DM, there is,

Table 3: General characteristics and biochemical parameters and indices of the male and female groups*

| | Males n = 19 | | | Females n = 14 | | |
|---|---|---|---|---|---|---|
| Variable | Before | After | p-value | Before | After | p-value |
| Fasting blood glucose (mg/dL) | 190.9±18.8 | 152.3±15.1 | 0.4 | 150.3±15.3 | 123.6±10.5 | 0.2 |
| Glycosylated hemoglobin (%) | 8.3±0.5 | 8.4±0.6 | 0.4 | 7.4±0.4 | 7.0±0.3 | 0.5 |
| Serum insulin (μU/ml) | 17.7±5.8 | 8.2±1.04 | <0.0001 | 14.9±4.0 | 9.9±2.1 | 0.03 |
| HOMA-IR | 8.6±3.3 | 3.1±0.5 | <0.0001 | 5.8±2.0 | 3.2±0.9 | 0.006 |
| HOMA-beta (%) | 2.0±0.5 | 1.3±0.2 | 0.0001 | 2.3±0.6 | 1.8±0.4 | 0.2 |
| QUICKI | 0.31±0.01 | 0.36±0.02 | <0.0001 | 0.32±0.01 | 0.34±0.01 | 0.4 |
| Serum calcium (mg/dL) | 9.5±0.1 | 8.9±0.1 | 0.02 | 9.6±0.1 | 9.0±0.1 | 0.9 |
| Parathyroid hormone (ρg/mL) | 58.7±5.1 | 52.1±5.9 | 0.6 | 81.2±5.9 | 82.5±16.8 | 0.001 |
| Serum vitamin D (nmol/L) | 34.5±2.6 | 70.7±7.5 | <0.0001 | 26.4±2.3 | 64.4±10.0 | <0.0001 |

HOMA-IR: Homeostasis model assessment-insulin resistance; HOMA-beta: Homeostasis model assessment-beta secretion; QUICKI: Quantitative insulin sensitivity check index. *Mean±SEM, p-value significant at <0.05

Table 4: Correlation coefficients (r) between serum vitamin D and the studied biochemical variables

| | r-value | | |
|---|---|---|---|
| Variable | Whole sample (n = 33) | Males (n = 19) | Females (n = 14) |
| Fasting blood glucose (mg/dL) | 0.04 | -0.05 | 0.3 |
| Glycosylated hemoglobin (%) | 0.1 | 0.1 | 0.06 |
| Serum insulin (μU/mL) | -0.4* | -0.3* | -0.5* |
| HOMA-IR | 0.2* | 0.1* | 0.3* |
| HOMA-beta (%) | 0.2 | 0.3 | 0.5* |
| QUICKI | -0.2 | -0.1 | 0.4* |
| Serum calcium (mg/dL) | 0.2 | 0.1 | 0.3 |
| Parathyroid hormone (ρg/mL) | -0.3* | -0.3* | -0.3* |

HOMA-IR: Homeostasis model assessment-insulin resistance; HOMA-beta: Homeostasis model assessment-beta secretion; QUICKI: Quantitative insulin sensitivity check index. p-value significant at <0.05

nevertheless, enough evidence to suggest a need to maintain 25 (OH) D levels in T2DM patients to not less than 30 ng/mL over the course of the year (Cavalier *et al*., 2011).

**Conclusion:** From the results of this study it can be concluded that improvement of vitamin D status is important for diabetic persons. Supplementation of vitamin D, although given for only one month, resulted in improvements of many diabetic indices in diabetic subjects with insufficient vitamin D status as well as changing the vitamin level to normal status.

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