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Beneficial Role of Vitamin D Supplementation on Thyroid Hormone Levels among T2DM Patients with Thyroid Disorders: Statistical Evaluation

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ABSTRACT

Thyroid function is impaired by diabetes, resulting into thyroid disorders, accompanied by the alteration of thyroid-stimulating hormone (TSH) and thyroxine (T_4) levels. The aim of this study was to investigate the role of vitamin D supplementation on TSH and total T_4 levels in serum of Libyan patients suffering from type 2 diabetes mellitus (T2DM) with thyroid disorders. A total of 180 subjects were recruited and distributed into two groups: 80 participants in control group (43 females and 37 males), with an age range of 26-72 years, and 100 participants in T2DM patient group (54 females and 46 males), with an age range of 26-63 years. Each T2DM patient received a monthly intramuscular injection of 200000 ng/ml vitamin D for three months. Glucose, vitamin D, total T_4 and TSH levels were determined in serum samples of healthy subjects and of T2DM patients (pre- and post-administration of vitamin D). After the T2DM group received vitamin D supplementation, the mean of vitamin D level increased in the T2DM, while the mean of glucose level decreased. Most importantly, the mean of total T_4 level for patients increased significantly ($p < 0.05$) from 1.34 to 8.23 μg/dL, both of which were lower than the control group mean 10.99 μg/dL. In contrast, the mean of TSH level for patients decreased significantly ($p < 0.05$) from 11.77 to 2.71 mU/L, and both values were greater than the control group mean 2.01 mU/L. ANOVA results showed that age, gender, and body mass index had no significant individual interactions ($p > 0.05$) with vitamin D supplementation on total T_4 and TSH levels. Vitamin D supplementation had a beneficial role on total T_4 and TSH levels in serum of Libyan T2DM patients with thyroid disorders.

Keywords: T2DM, thyroid disorder, total T_4, TSH, vitamin D supplementation, ANOVA, *t* test.

1. INTRODUCTION

In recent years, attention has been drawn to the role of vitamin D in areas other than bone metabolism and calcium homeostasis. This vitamin is a steroid produced by skin and contributes to the expression regulation of various genes [1]. Since the primary action of this vitamin is to regulate calcium and phosphorus homeostasis and control of bone metabolism [1, 2], its deficiency is linked to skeletal diseases such as rickets, muscle weakness and skeletal mineralization defect [3]. However, vitamin D has been shown in several studies to be associated with the risk of non-skeletal diseases such as cardiovascular disease,

cancer [1, 4], type 2 diabetes mellitus (T2DM) [1,5], and thyroid disorders (TD) including Hashimoto's thyroiditis (HT) and Graves' disease (GD) [6, 7].

For humans, the main sources of vitamin D are diet (particularly fish), fortified food, supplements, and exposure to sunlight [8, 9]. Its activity is mediated by the interaction with vitamin D receptors (VDR), which further leads to activation of various genes [5, 7, 10]. These receptors are endocrine members of nuclear receptors that represent a family of important transcription factor, and it is well known that VDR present in nearly all body tissues such as intestine, kidney, skin and the thyroid gland [11]. There are two major forms of vitamin D which are: vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Although these two forms differ slightly in their structures in the side chain, their metabolism routes in human body are identical [12]. Both of these forms are transported through blood stream to the liver where they are metabolized to 25(OH) D, which is further metabolized in the kidney to the biologically active form 1, 25 dihydroxy vitamin D (1, 25-$(OH)_2$ D) [5, 7, 8]. And as 25(OH) D form has a longer half-life compared to 1, 25-$(OH)_2$ D form, therefor the former form is the most widely accepted biomarker of vitamin D status in human body [13].

According to serum level of 25(OH) D, vitamin D status in adults is defined as follows: >30 ng/ml is considered as sufficient; 20-29 ng/ml as insufficient vitamin D, <20 ng/ml as vitamin D deficiency [5, 8, 9] and <10 ng/ml is considered an evidence of severe vitamin D deficiency [14]. Few studies have documented that vitamin D deficiency occurs in T2DM patients suffering from TD [15-17], which has been reported to coexist in T2DM patients, and this coexistence results into patient health deterioration [18-20]. Thyroid function is impaired by diabetes through affecting the thyroid-stimulating hormone (TSH) level and impairing the synthesis of triiodothyronine (T_3) from thyroxine (T_4) [18].

In Libya, an Arab country located south of the Mediterranean Sea and one of the Middle East and North Africa Region countries, there is a limited number of studies in which the comorbidity of T2DM and TD has been addressed. Compared to other countries, the prevalence of TD in T2DM Libyan patients (9.5%) has been found to be lower in a study conducted in Surman, a city located at west of Libya. This study has also revealed that thyroid disorders are more common in females to males (16.5:1 fold) [21].

To the best of our knowledge, no clinical trial has been conducted in Libya to investigate the role of vitamin D supplementation in improving the levels of thyroid hormone in T2DM patients suffering from TD. Thus, this study was conducted to statistically evaluate the role of vitamin D supplementation on thyroid stimulating hormone (TSH) and total thyroxine (T_4) in T2DM Libyan patients with abnormal values for both hormones. Additionally, the interaction of gender, age and body mass index (BMI) with the supplementation was investigated.

2. MATERIALS AND METHODS

The permission to conduct this study was granted by the Bioethics Committee at the Libyan Center for Biotechnology Research, Tripoli, Libya, under the ethics reference number (BEC-BTRC 20-2021). Informed consent was obtained from all subjects participated in this study after being informed of the study procedure.

2.1 Subjects

This research was carried out in Libya's capital, Tripoli, and started in June 2019. A total of 180 subjects was recruited and distributed into two groups: control group and T2DM patient group. The control group comprised of 80 healthy subjects of both genders (43 females and 37 males). Routine clinical tests showed that none of the subjects of this group was affected by any diseases. Additionally, there was no history of thyroid disease or any other chronic

ailment that could have influenced the study's findings. In the case of T2DM patient group, the total number was 100 patients (54 females and 46 males) and these patients were known to have abnormal levels of TSH and total T_4.

2.2 Supplementation administration and evaluation of its effect

To evaluate the influence of vitamin D on TSH and total T_4 levels, each T2DM patient received a monthly intramuscular injection of 200000 ng/ml vitamin D for three months. The control group participants had not received vitamin D injections. Serum samples of healthy subjects and of T2DM patients (pre- and post-administration of vitamin D supplementation) were obtained and analyzed for their content of total T_4, TSH, vitamin D and glucose.

2.3 Blood Samples Collection

In the case of the control group, one serum sample was analyzed for each subject, whereas two serum samples were analyzed for each patient in the case of the patient group: one on the first day of the trial (before vitamin D administration) and the other three months later (after vitamin D administration)

After 12-14 hours of fasting, venous blood samples were collected in plain vials and processed within 24 hours. Each venous blood sample was centrifuged for 5 minutes at 3000 rpm, then the obtained serum was transferred to a clean specimen tube and stored at -20 °C.

2.4 Biochemical analysis

Serum total T_4, TSH, vitamin D and glucose levels were measured once for each subject of the control group, and twice for each subject of the patient group, pre- and post-administration of vitamin D supplementation. All the measurements were done in triplicate and the average was calculated.

Vitamin D was analyzed according to the kit instructions using ichroma™ II (Boditech Med Incorporated, Gangwon-do, Korea), and the method was competitive fluorescence Immunoassay (FIA). In this method, the target material in the sample binds to a fluorescence (FL)-labeled detection antibody, forming a complex. This complex is loaded to migrate onto the nitrocellulose matrix, where vitamin D is immobilized on a test strip, and interferes with the binding of target material and FL-labeled antibody, then the fluorescent intensity is measured

Analyzing serum for its content of glucose was carried out according to the kit instructions using KENZA MAX BioChemisTry Analyser (Biolabo Diagnostics, Kenza Biochemistry TM, France). Glucose oxidase (GOD) oxidizes glucose to D-gluconate, which is accompanied by formation of hydrogen peroxide, that reacts with a mixture of phenol and 4-aminoantipyrine (4-AA) in the presence of peroxidase (POD) resulting into formation of quinoneimine. The absorbance of quinoneimine, measured at 500 nm, is directly proportional to the content of glucose.

Measurement of TSH and total T_4 levels was performed using ichroma™ II (Boditech Med Incorporated, Gangwon-do, Korea). The applied methods for measuring TSH and total T_4 were carried out according to the manufacturer's protocol.

For TSH, the sandwich immunodetection method was used in which a detector antibody is coupled to antigen in the sample, leading to formation of antigen-antibody complex that moves onto nitrocellulose matrix to be retained on another immobilized-antibody on test strip. The antigen-antibody complex leads to a fluorescence signal on detector antibody, and the signal intensity is proportional to the amount of the antigen in present, and it is expressed as TSH concentration.

For total T_4, the competitive immunodetection method was used. In this method, the target material in the sample binds to a fluorescence (FL)-labeled detection antibody, producing a complex that migrates onto the nitrocellulose matrix,

where it is immobilized on a test strip, and interferes with the binding of target material and FL-labeled antibody, then fluorescent intensity is measured.

2.5 Statistical analysis

A set of some descriptive statistics was calculated. They were the mean, standard deviation, and coefficient of variation (CV%), as well as the minimum (Min) and maximum (Max) values. This set of descriptive statistics was calculated for all study variables: total T_4, TSH, Glucose, pre- and post- supplement administration, as well as BMI and age.

Also, paired *t* test was performed to compare the means of total T_4, TSH, and glucose levels in patient group, pre- and post- supplement administration (significant if $p>0.05$). On the other hand, unpaired *t* test was performed to compare the means of total T_4, TSH, and glucose levels in patient groups before and pre- and post- supplement administration, with their means in control group (significant if $p > 0.05$).

Finally, Two-way repeated measures ANOVA was performed to determine if there was an interaction between the covariates (age, gender, and BMI) and the effect of vitamin D supplement on total T_4, TSH, and glucose levels. A p value of <0.05 was considered statistically significant.

3. RESULTS

3.1 Results of descriptive statistics

Table 1 shows descriptive statistics of age and body mass index (BMI) for both of control and patient groups. The descriptive statistics included: the mean, standard deviation (SD), coefficient of variation (CV%), minimum (Min) and maximum (Max) values.

Table 1 Descriptive statistics of age and BMI for control and patient groups

		Mean	SD	CV%	Min	Max
Control group	Age (years)	41.59	9.36	22.51	26.00	72.00
	BMI (Kg/m^2)	23.30	0.98	4.20	21.30	27.80
Patient group	Age (years)	42.47	8.78	20.68	26	63
	BMI (Kg/m^2)	26.66	2.09	7.83	21.70	31.90

The mean and CV of age and of BMI for both groups were close to each other, indicating that the variation in these two factors would not affect the findings of this study.

As indicated in Table 2, the descriptive statistics of the clinical data for patient group compared to control group revealed an improvement of their biochemical values following vitamin D treatment. The mean of vitamin D level in the patients increased from 8.59 ng/mL to 40.11 ng/mL, which was greater than the control group's mean of 30.37 ng/mL. Patients' mean glucose levels, on the other hand, dropped from 152.59 to 135.60 mg/dL, both of which were greater than the control group's mean of 86.48 mg/dL.

Table 2 Descriptive statistics of clinical data for control group, patient group before vitamin D administration (Patient group BV) and patient group after vitamin D administration (Patient group AV).

		Mean	SD	CV%	Min	Max
Vitamin D (ng/mL)	Control group	30.37	3.04	10.00	22.22	41.77
	Patient group BV	8.59	3.27	38.02	4.09	23.12
	Patient group AV	40.11	13.10	32.65	19.00	68.77
Glucose (mg/dL)	Control group	86.48	5.08	5.87	77.77	99.43
	Patient group BV	152.59	17.25	11.31	119.00	197.00
	Patient group AV	135.60	13.09	9.66	100.00	183.00
TSH (mU/L)	Control group	2.01	0.73	35.99	0.60	3.91
	Patient group BV	11.77	2.27	19.33	8.01	19.01
	Patient group AV	2.71	1.18	43.49	1.01	5.22
Total T_4 (µg/dL)	Control group	10.99	0.95	8.66	8.35	12.53
	Patient group BV	1.34	0.79	58.59	0.01	3.09
	Patient group AV	8.23	1.72	20.91	4.02	12.54

After receiving vitamin D supplementation, the mean of total T_4 level for patients increased from 1.34 to 8.23 g/dL, both of which were lower than the mean in control group 10.99 g/dL. In contrast, the mean of TSH level for patients decreased from 11.77 to 2.71 mU/L, and both values were greater than its mean in control group 2.01 mU/L.

3.2 Results of *t* test

According to results of paired *t* test, shown in Table 3, the mean difference of total T_4 and TSH levels for patient group, pre- and post-administration of vitamin D, was significant ($p < 0.05$).

Table 3 Results of paired *t* test for TSH and total T_4 means in patient group: before and after administration of vitamin D.

	T-Value	P-Value
Total T_4	38.17	0.000
TSH	36.02	0.000

When total T_4 and TSH levels of patient group, pre- and post-administration of vitamin D, were compared to those for the control group using unpaired *t* test, it was found that the mean differences for both hormones were significant ($p < 0.05$) (Table 4).

Table 4 Results of unpaired t test: comparison of TSH and total T_4 level means in control group with patient group vitamin D administration (Patient group BV) and group after vitamin D administration (Patient group AV).

		T-value	P-value
Total T_4	Control group / Patient group BV	72.88	0.000
	Control group / Patient group AV	12.84	0.000
TSH	Control group / Patient group BV	17.38	0.000
	Control group / Patient group AV	4.62	0.000

3.3 Results of ANOVA

The results of Two Way ANOVA (Within-Subjects Effects) confirmed the results of unpaired *t* test as it revealed that there was significant difference (p=0.000, significant as it was < 0.05) between the levels of each of total T_4, TSH and vitamin D, pre- and post-administration of the supplement. Furthermore, the value of partial eta squared (η^2) was 0.729, indicating a large effect. In other words, vitamin D supplementation improved the levels of these biochemicals.

There was no significant individual interactions ($p > 0.05$) between any of the three factors (age, gender and BMI) and the administration of vitamin D on the levels of the three biochemicals (total T_4, TSH and vitamin D). However, there was an interaction between both of gender and BMI with the administration vitamin D on the levels of the three biochemical (p=0.024, significant as it was < 0.05).

4. DISCUSSION

Total thyroxine (T_4) is one of the vital hormones synthesized in thyroid gland, this hormone, along with other hormones produced by thyroid gland, are responsible for dietary metabolism regulation in the human body [22]. The pituitary gland controls the synthesis of these hormones through the Thyroid Stimulating Hormone (TSH), which is responsible for regulating thyroid gland [23]. The increase in TSH leads to Hypothyroidism, with the symptoms of: weight gain, feeling sad and cold, pain in the joints and hair loss [24]. The high level of TSH is related to the dysfunction of the thyroid gland in producing T_4 and other hormones that control the metabolism [25].

Vitamin D deficiency and thyroid diseases are highly correlated among T2DM patients [26, 27]; the results of this study showed that vitamin D supplementation could improve the regulation of the thyroid hormones among T2DM Libyan patients. Similar studies reported negative relationship between serum 25(OH)D levels and serum thyroid stimulating hormone (TSH) levels [28-30].

The descriptive statistics (Table 2) in general showed improvement in the biochemical values among T2DM patients after vitamin D administration compared with these values before introducing the vitamin D supplementation. This is because high doses of vitamin D could improve the

insulin resistance and control the blood sugar in patients with type 2 diabetes [31]. In addition, vitamin D improved the thyroid gland function, which plays an important role in the metabolism of fat and carbohydrates and influences diabetes [20].

According to the results of paired *t* test in this study, the mean difference of total TSH level for patient group, pre- and post-administration of vitamin D, was significant, which revealed a significant negative relationship between TSH level and Vitamin D in the patient group. This could be due to the important role of vitamin D in maintaining the thyroid gland by controlling the interaction with its receptors (VDR) in this gland [32, 33]. This relationship was also emphasized by the results of ANOVA.

In addition, paired *t* test and ANOVA results of the comparison of T_4 means in patient group; before and after administration of vitamin D; indicated a significant relationship between the two means. The present study revealed an increase in T_4 hormone in the patient body after receiving vitamin D supplement. All of these findings suggested that vitamin D is important, acting at central level for pituitary gland function, also balancing type 2 deiodinase (DIO2) expression at thyroid and thus affecting peripheral conversion of T_4 into T_3 [34].

The results of ANOVA showed that there was an interaction between both of BMI and gender with the administration vitamin D on the levels of the three biochemicals ($p=0.024$, significant as it was <0.05). This could be due the fact that body adipose tissues act as a reservoir for lipid-soluble vitamin D, which protect the body from toxic effects of the active forms of vitamin D and maintain its level in the blood serum. The accumulation of this Vitamin in the body fat is faster than its release to the serum, which means that there is an inverse relationship between serum vitamin D and the BMI [35].

Females and males with the same BMI have different fat content. Studies have found that on average, Females have 10-15% more fat content than males [36, 37]; which means that more vitamin D will be stored in female fat tissue after cutaneous synthesis and less will stay in the blood; this could explain the reason behind vitamin D deficiency prevalence among females [38, 39].

This study was the first randomized controlled clinical trial in Libya, which evaluated the effects of Vitamin D supplementation in improving Level of TSH and total T_4 among T2DM Libyan patients who are suffering from thyroid dysfunction. The results of this study revealed that the treatment with vitamin D has improved significantly the T_4 and TSH levels among those patients.

5. CONCLUSION

This study proved that vitamin D supplementation had a beneficial role on total T_4 and TSH levels in serum of T2DM patients with thyroid disorders. Similar study is required to compare the effect of vitamin D supplementation on TSH, T_4 and T_3 levels. Also, other studies are needed in which other biochemical levels, such as triglycerides and cholesterol, will be investigated and linked to the alteration of TSH, total T_4 and T_3 levels in serum of T2DM patients with thyroid disorders supplemented with vitamin D.

6. Limitations of the study

The role of vitamin D supplementation on the level of T_3 was not investigated in the current study. The evaluation of this role may reveal more important outcomes, which can be employed by specialists.

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