Influence of vitamin D supplementation on glycemic control in type 2 diabetics

Influence de la supplementation en vitamine D sur l'équilibre glycémique des diabétiques de type 2

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RÉSUMÉ

Introduction : Plusieurs études suggéraient le bénéfice de la supplémentation en vitamine D sur le contrôle glycémique et l'insulinorésistance chez les diabétiques de type 2. Les objectifs de notre travail étaient d'apprécier le taux de vitamine D dans une population de diabétiques type 2 et d'évaluer l'effet de la supplémentation en vitamine D sur l'équilibre glycémique des patients déficitaires.

Méthodes : Il s'agissait d'une étude prospective qui a concerné 100 patients diabétiques de type 2 suivis à l'Institut National de Nutrition et de Technologie Alimentaire de Tunis. Le contrôle glycémique et l'insulinorésistance ont été évalués au début de l'étude et 3 mois après la supplémentation.

Résultats : La concentration sérique moyenne en 25(OH)D était de 17,5±9,8 ng/ml. Le statut vitaminique D était normal chez 14 % de nos patients. L'insuffisance et la carence en vitamine D étaient présentes chez 60 % et 26 % des patients respectivement. Après la supplémentation en vitamine D, les taux moyens de 25(OH)D ont significativement augmenté ($P < 10^{-3}$). Nous avons observé une correlation négative entre les variations de la vitamine D et du tour de taille (r=-0,266 et P=0,018). Cette corrélation persiste même après ajustement sur les modifications thérapeutiques. La supplémentation en vitamine D n'a pas entrainé d'améliorations significatives de l'équilibre glycémique et des paramètres d'insulinorésistance.

Conclusion : Le déficit en vitamine D est fréquent chez les diabétiques de type 2. Les effets métaboliques de la supplémentation sont encore controversés d'où la nécessité d'élargir les études afin de mieux démontrer ces effets.

Mots-clés

Diabète type 2, insulinorésistance,antidiabétiques oraux, vitamine D, déficit

SUMMARY

Introduction: Several studies have suggested a benefic impact of vitamin D supplementation on glycemic control and insulin resistance among patients with type 2 diabetes mellitus. The aims of our study were to assess vitamin D status in individuals with type 2 diabetes mellitus and to investigate the effects of vitamin D supplementation on glycemic measures in patients having vitamin D deficiency.

Methods: We conducted a comparative prospective study involved 100 Tunisian patients with type 2 diabetes followed at the National Institute of Nutrition and Food Technology of Tunis. Glycemic control and insulin resistance were evaluated in the beginning of the study and three months after supplementation.

Results: Baseline mean 25-Hydroxy vitamin D (25(OH)D) level was 17.5±9.8 ng/ml. Vitamin D status was deficient in 60%, insufficient in 26% and sufficient in 14% patients. After vitamin D supplementation, mean serum 25(OH)D concentration increased significantly ($P < 10^{-3}$). We observed a negative correlation between the variation of plasma 25(OH)D level and the waist circumference's variation (r=-0.266 and p=0.018). This correlation persisted after adjustment for therapeutic management. Vitamin D supplementation did significantly improve neither glycemic control nor insulin resistance parameters.

Conclusion: Vitamin D deficiency is frequent in patients with type 2 diabetes mellitus. The metabolic effects of supplementation are controversial, hence the need of expanding studies to better demonstrate these effects.

Key-words

Diabetes Mellitus type 2, Insulin Resistance, drug therapy, vitamin D, deficiency

INTRODUCTION

Vitamin D is a fundamental micronutrient with major implications for human health. The major and most well-known function of vitamin D is to maintain calcium and phosphorus homeostasis and promote bone mineralization (1). However, recent evidence suggests that vitamin D may also be important for a variety of no skeletal outcomes including neuromuscular function and falls, psoriasis, multiple sclerosis and cancer (2). Several studies have also showed the role of vitamin D in the pathogenesis of type 2 diabetes mellitus (T2DM). The link of vitamin D with insulin insensitivity or abnormal glucose metabolism gained much more scientific attention during the last decade (3).

It has been demonstrated that the incidence of vitamin D deficiency is higher in diabetic patients. The serum 25-Hydroxy vitamin D (25(OH)D) concentration was shown to be inversely correlated with the prevalence of type 2 diabetes and insulin resistance (4).

The aims of our study were to assess the vitamin D levels in a Tunisian population with type 2 diabetes and to investigate the effect of vitamin D supplementation on glycemic control in patients with vitamin D deficiency.

METHODS

Study design

We conducted a prospective study among patients with type 2 diabetes mellitus who were followed at the National Institute of Nutrition and Food Technology of Tunis from May 2013 until August 2014. The study was approved by the Ethics Committee of the National Institute of Nutrition and Food Technology and an oral informed consent was obtained from all patients for participation in this study. We enrolled patients, aged between 35 and 75 years, having type 2 diabetes mellitus since at least three years and being treated with oral antidiabetic drugs. We didn't include patients with type 1 diabetes mellitus or insulin-requiring diabetes, patients with hyperparathyroidism or active cancer disease, patients with known metabolic bone disease, laboratory evidence of kidney (estimated glomerular filtration rate <50 ml/min) or liver disease, patients taking drugs that affect vitamin D metabolism and pregnant women. Two clinical visits were planned for each included patient (T0 at baseline and T1 three months after the end of vitamin D supplementation).

Clinical and biochemical Analysis

Demographic characteristics, diabetes mellitus history, comorbidities and smoking habits were determined on the basis of an interview. Anthropometric parameters (weight, height and waist circumference) and biochemical measurements were evaluated at the beginning (T0) and the end of the study (T1). BMI (kg/m2) was calculated as weight (kilograms) divided by height (metres) squared. Fasting blood glucose and HbA1c was measured using glucose oxidase method and high performance liquid chromatography method respectively. The blood level of 25(OH)D was measured by enzyme immunoassay at the Clinical Biology Laboratory of the Institute of Nutrition. Vitamin D deficiency was defined as serum 25(OH)D concentrations <10 ng/ml, vitamin D insufficiency was defined as serum 25(OH)D concentrations 10–30 ng/ml, and vitamin D sufficiency was defined as serum 25(OH)D concentrations >30 ng/mL (5). Fasting serum insulin was measured by enzyme immunoassay. To evaluate insulin resistance, we have calculated HOMA-IR and HOMA-β.

HOMA-IR was used to evaluate insulin resistance, it was calculated according to the following formula: fasting serum insulin (µU/ml) × fasting plasma glucose (mmol l/)/22,5 (6). HOMA-β was used to evaluate insulin secretion, it was calculated according to the following formula: fasting serum insulin (µU/ml) ×20 / fasting plasma glucose (mmol /l) - 3,5 (6).

Supplementation protocol

Patients with vitamin D deficiency have received vitamin D supplementation according to the initial level of 25 (OH) D:

• One unique dose of 200 000 IU of vitamin D3 was given in case of 25(OH)D level ≥ 20 and < 30 ng/ml.

• One dose of 200 000 IU of vitamin D3 and a second dose one month after, were given in case of 25(OH)D < 20 ng/ml.

Statistical analysis

The statistical analyses were performed using Statistical Program for Social Sciences, SPSS 19.0. All results were expressed as mean ± standard deviation for quantitative variables and as percentages for qualitative variables. The comparison of means before and after supplementation was analyzed using the student's t-test. Pearson correlation coefficients between continuous variables were used as a measure of association. A p value less than 0.05 was considered significant.

Statement of Ethics

Ethical approval: All procedures performed in this study were in accordance with the ethical standards of the responsible committee on human experimentation and were approved by the Ethics Committee of the National Institute of Nutrition and Food Technology of Tunis.

Informed consent: Informed consent was obtained from all individual participants included in the study.

RESULTS

The baseline characteristics of the participants are represented in Table 1. Regarding vitamin D status, serum 25(OH)D levels ranged from 4 to 46.4 ng/ml with a mean of 17.5±9.8 ng/ml in the whole group of the 100 patients included in the study. Vitamin D status was deficient in 60%, insufficient in 26% and sufficient in 14% of patients. After vitamin D supplementation in deficient and insufficient patients, we have observed a significant improvement in serum levels of 25(OH)D (Table 2). However, we did not observe a significant improvement in glycemic control after vitamin D supplementation. Mean insulinaemia and HOMA-IR index decreased slightly but not significantly. The HOMA-β index declined showing the decrease in insulin secretion (Table 3).

Table 1: Baseline characteristics of the participants (n =100)

Baseline characteristics	Total (n=100)
Age (years)	56.4 ± 8.4
Sexe Ratio (M/F)	0.79
Current Smoking (%)	28.6
BMI (Kg/m2)	30.5 ± 5.7
Obesity (%)	50
Waist circumference (cm)	
Male	101.5 ± 11.6
Female	100.9 ± 12.3
Duration of diabetes (years)	7 ± 3.8
Oral antidiabetic drugs (%)	
Metformin	91
Sulfonylurea	67
Fasting glucose (mmol /l)	8.3 ± 2.4
Mean of HbA1c (%)	7.6 ± 1.4
HbA1c ≤ 7% (%)	33
Comorbidities (%)	
Hypertension	64.4
Dyslipidemia	87

Table 2: Vitamin D level before and after supplementation in patients with type 2 diabetic patients according to vitamin D status (n=86)

25 (OH) D	T0	T1	Delta	P value
Mean value (ng/ml)	14.5 ± 5.9	33.0 ± 8.7	18.4 ± 8.9	<10-3
[10-30[ng/ml	17.0 ± 4.8	34.5 ± 9.2	17.5 ± 4.4	<10-3
<10 ng/ml	8.1 ± 1.7	29.3 ± 6.1	21.2 ± 4.4	<10-3

25 (OH) D: 25-Hydroxy vitamin D

Table 3: The effect of vitamin D supplementation on anthropometric measurements, glycemic control and insulin sensibility parameters (n=86)

	T0	T1 Delta	P	value
BMI (Kg/m²)	30.8 ± 5.9	30.9 ± 6.1	0.1 ± 1.2	NS
WC (cm)	100.3 ± 11.1	99.8 ± 11.6	-0.4 ± 4.2	NS
Glucose (mmol/l)	8.2 ± 2.3	8.6 ± 2.6	0.4 ± 1.9	0.045
HbA1c (%)	7.6 ± 1.5	7.8 ± 1.5	0.2 ± 1.4	NS
Insulin (µUI/ml)	10.1 ± 7.4	8.8 ± 5.9	-1.29 ± 6.8	NS
HOMA-IR	3.6 ± 3.1	3.3 ± 2.5	-0.3 ± 3.0	NS
HOMA-β	55.4 ± 51.0	43.2 ± 38.7	-12.2 ± 41.4	0.015

BMI: Body mass index, WC: Waist circumference

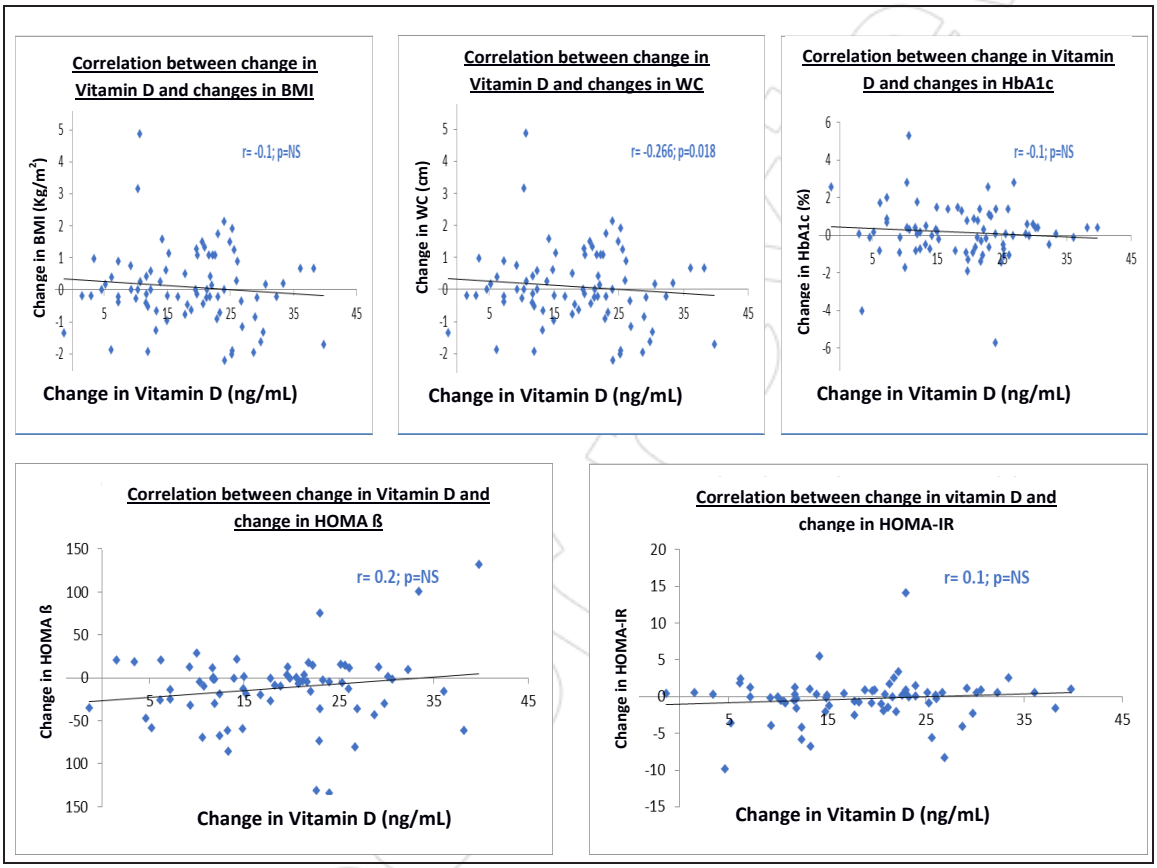
During the follow-up of the study, antidiabetic drug regimens were management for almost 33% of the patients having received vitamin D supplementation. In order to overcome this bias, we had analyzed the results of the group of patients whose treatment remained unchanged (n=58). But HbA1c remained almost stable (Table 4).

Correlations between the variation in vitamin D and the changes in BMI, waist circumference, HbA1c, HOMA-IR index and HOMA-β index are represented in figure 1.

Table 4: The effect of vitamin D supplementation on glycemic metabolism in the group with unchanged treatment (n=58)

	T0	T1	P value
Glucose (mmol/l)	7.9 ± 2.2	8.2 ± 2.3	NS
HbA1c (%)	7.4 ± 1.5	7.3 ± 1.0	NS
Insulin (µUI/ml)	10.2 ± 8.0	8.5 ± 5.0	NS
HOMA-IR	3.7 ± 3.4	3.1 ± 2.0	NS
HOMA-β	56.3 ± 49.6	46.8 ± 41.6	NS
BMI (Kg/m2)	31.3 ± 6.5	31.2 ± 6.7	NS
WC (cm)	101.1 ± 11.1	99.9 ± 11.1	0.038

BMI: Body mass index, WC: Waist circumference.



BMI : Body Mass Index ; WC : Waist Circumference.

Figure 1: Correlation between change in vitamin D and changes in clinico-biologic characteristics.

DISCUSSION

In our study, the majority of our patients had vitamin D deficiency. The average serum level of 25 (OH) D among T2DM subjects was significantly improved three months after the vitamin D supplementation. Our results were in agreement with previous studies (7-10). However, despite this improvement, we did not observe significant improvement in glycemic control which confirms the finding of several studies (8, 9, 11-14). In Switzerland, the administration of a single dose of 300,000 IU vitamin D3 in 55 type 2 diabetics with hypovitaminosis D (<50 nmol/l) was paradoxically accompanied by a non-significant increase of HbA1c. This increase was less marked in the group receiving vitamin D (+2.9%±1.5%) compared to the placebo group (+6.9%±2.1%), p=0.04 (15). Besides, Witham et al (13) conducted a randomised controlled trial to compare the effect of 100,000 and 200,000 IU doses of vitamin D on markers of glycemic control in diabetic patients. The results showed that high-dose vitamin D did not improve insulin resistance or glycosylated hemoglobin in patients with type 2 diabetes. In addition, it had been demonstrated that the extension of the supplementation period to 6 months did not also have a benefic effect on glycemic parameters (11). A meta-analysis summarizing 15 clinical trials evaluating the effect of vitamin D supplementation on glycemic control and insulin resistance in type 2 diabetic versus placebo concluded that vitamin D supplementation result in minimal improve of fasting glucose and insulin resistance but does not change HbA1c (16).

However, some studies have shown significant improvement in glycemic control. Nasri et al (17) have conducted a double-blind clinical trial in Iran where 60 patients with type 2 diabetes who received weekly vitamin D supplementation of 50,000 units of vitamin D3 for 12

weeks were compared to a control group. HbA1c in the supplement group was significantly lower than that in the control group. The use of lower doses of vitamin D for shorter durations (50000 units / week of vitamin D3 for 8 weeks) had shown a beneficial effect on diabetic glycemic control in some studies (18). According to Tabesch et al (19) Calcium-vitamin D co- supplementation may lead to a significant reduction in HbA1c. A recent systematic review found that vitamin D supplementation is associated with a reduction in HbA1c levels in studies with long-term intervention durations (20). As it was shown, the results of previous vitamin D supplementation intervention studies have been inconsistent. The disparity may be explained by differences in patients' baseline characteristics (baseline 25(OH)D level, concomitant calcium supplementation, BMI, length of intervention, and change of 25(OH)D concentration after supplementation). The improvement of glycemic control can be attributed to Vitamin D actions on beta cells (21, 22). Vitamin D may increase insulin secretion and reduce peripheral insulin resistance (23). Vitamin D also has an inhibitory effect on the production of some cytokines (24). It can therefore modulate inflammation, which would be involved in insulin resistance, type 2 diabetes mellitus and even in apoptosis of pancreatic beta cells (25). More recent evidence suggests that control of the adiponectin gene by calcitriol may also explain the influence of vitamin D on insulin resistance (26).

Concerning the impact of vitamin D supplementation on insulin resistance, results are very variable. In our study, we did not find significant effects of vitamin D supplementation on insulin sensitivity or on insulin resistance. The decrease in HOMA-β cannot be only attributed to the effect of vitamin D. It can be explained by the natural history of diabetes and the stage of insulinopenia in these patients, as they needed therapeutic reinforcement in 33% of cases. Several studies have not reported significant changes in insulin and HOMA-IR after vitamin D supplementation (9). A negative effect on insulin resistance was even noted in the Saudi Arabian study of 120 type 2 diabetics who received 2000 IU vitamin D3 daily for 18 months. A significant increase in the HOMA-IR index from 6.2±1.0 to 11.4±1.4 after 18 months of supplementation (P<0.001) was observed (10). Nerveless, other studies have demonstrated a positive effect of vitamin D supplementation on insulin resistance (18) and insulin secretion (9). Insulin secretion and sensitivity are complex parameters that depend on several factors (fat mass, stage of disease, physical activity...) and which require more sophisticated means such as the realization of euglycemic clamps.

Regarding anthropometric measurements, we did not find any significant change in BMI after vitamin D supplementation. However, we noticed a decrease in waist circumference. In the literature, the effects of vitamin D supplementation on anthropometric parameters were contradictory. In a randomized clinical trial, daily intake of vitamin D-fortified yoghurt, with or without calcium, has resulted in a decrease in BMI and waist circumference in type 2 diabetics (27). However, in the study by Al Sofiani et al (9) changes in BMI and waist circumference were not significant after vitamin D supplementation. On the other hand, in the Saudi study of Al Daghri et al (10) the BMI even increased but not significantly from 32.5±5.0 kg / m2 to 33.2±5.2 kg / m2 after 18 months of vitamin D supplementation.

Our work is the first in Tunisia to have evaluated the effect of vitamin D supplementation in type 2 diabetics. However, this study has some limitations. First, the lack of a placebo-control group and second, this study included only patients with T2DM.

CONCLUSION

Our data suggest that high-dose vitamin D supplementation might be effective in terms of elevating 25(OH)D levels. Further studies are needed, with the inclusion of a placebo group, to validate the present findings. The results of these future studies will define the clinical role of vitamin D as potential intervention for prevention and management of type 2 diabetes, which will have significant public health implications. As vitamin D insufficiency is common in adults, this intervention can be implemented easily and inexpensively in clinical practice.

Disclosure Statement All authors have no potential conflicts of interest relevant to this paper.

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