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Original Article

Association between vitamin D status and glycemic profile in postmenopausal women with type 2 diabetes

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ABSTRACT

The aim of this study is to evaluate the association between vitamin D status and glycemic profile in postmenopausal women with type 2 diabetes. A cross-sectional study was carried out with 70 (59.47 ± 6.47 years; 1.56 ± 0.05 m; 73.56 ± 13.01 kg; 30.30 ± 5.00 BMI kg/m^2) postmenopausal women with type 2 diabetes (T2D). The blood samples were collected after fasting for 12 h and the main outcome parameters were serum follicle-stimulating hormone (FSH), estradiol; 25-OH vitamin D; insulin; C-Reactive Protein; cholesterol total (CT), triglycerides (TG), high density lipoprotein (HDL-cholesterol), glucose; calcium, HDL-cholesterol. The average serum 25(OH)D level in this study was 28.45 ± 8.26 ng/mL. The prevalence of hypovitaminosis D was 60%. Table 1 displays mean and standard deviation values for participants' characteristics. The postmenopause status of the women studied was confirmed by FSH and estradiol measurement. All the clinical and anthropometric characteristics did not show difference ($p > 0.05$) between the groups (Table 2). Triglycerides level was highest ($p < 0.0391$) in the hypovitaminosis D group. The other serum markers did not show statistical differences ($p > 0.05$) between the groups. In conclusion, our results suggest that only TG level shows a negative correlation with vitamin D status in postmenopausal women with type 2 diabetes.

1. Introduction

Vitamin D can be found in the form of ergocalciferol or vitamin D_2 and cholecalciferol or vitamin D_3. Vitamin D_2 can be obtained from some yeast and plants, being produced for commercial use, through irradiation of the ergosterol present in some mushrooms. In the skin, the precursor is the 7-dehydrocholesterol (7-DHC). During sun exposure, UVB photons (ultraviolet B, 290–315 nm) penetrate the epidermis and produce a photochemical fragmentation to originate pre-cholecalciferol. This intermediate is converted to vitamin D (or cholecalciferol) through a temperature-dependent isomerization [1,2].

Cholecalciferol is transported to the liver by DBP (vitamin D binding protein). In the liver, there is the hydroxylation of carbon 25 (CYP27B1), forming the 25-hydroxyvitamin D (25(OH)D), through a process which is not strictly regulated, since it happens without control, and depends on the combination of cutaneous and diet stocks of vitamin D. After the liver step, 25(OH)D is transported to the kidneys by DBP, where it is converted to calcitriol or 1,25-dihydroxyvitamin D [1,25(OH)2 D]. This is the most active metabolite and it is responsible for stimulating intestinal calcium and phosphate absorption [3].

Recently, vitamin D has risen as a potential diabetes risk modifier. The potentially significant extra-skeletal role of vitamin D is highlighted in several recently published studies, including the demonstration of the expression of the vitamin D receptor in a large number of non-skeletal cells, including pancreatic beta cells (MITRI AND PITTAS, 2014).

There are many cross-sectional studies that have examined the association between vitamin D status and type 2 diabetes. SCRAGG, SOWERS AND BELL [4] reported one of the largest such cohorts is the National Health and Nutrition Examination Survey (NHANES) in United States, which an inverse association between 25OHD concentration and prevalence of diabetes in non-Hispanic whites and

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Mexican-Americans, but not African-Americans.

Srimani, Saha and Chaudhuri [5] observed a significant negative correlation between fast blood glucose and 25(OH)D level in postmenopausal women in India. However, Wang et al. [6] studied the correlations of 25(OH)D with indices of glucose metabolism in female population (51.33 ± 10.24 years old) type 2 diabetes – no significant correlation were observed. Raška Jr. et al. [7] also showed there was no significant difference in glycated hemoglobin, fasting glucose or duration of diabetes between type 2 diabetes postmenopausal women with hypovitaminosis D and type 2 diabetes postmenopausal women with normal 25-OH D level.

The aim of this study is to evaluate the association between vitamin D status and glycemic profile in postmenopausal women with type 2 diabetes.

2. Methods

2.1. Research design

A cross-sectional study was carried out with 70 postmenopausal women with type 2 diabetes. These women were attended at the Female Endocrinology Outpatient Clinic of the National Institute of Women's, Children's and Adolescents' Health - Fernandes Figueira (IFF), Rio de Janeiro, RJ, Brazil. Women were recruited from a pre-existing database and later contacted by telephone or selected when identified at the time of consultation from the medical records analysis. They were recruited from August 2013 to August 2014. Vitamin D insufficiency was defined as 25(OH)D < 30 ng/ml, which is in accordance with the recommendation of World Health Organization [8].

All patients had previous experience in being treated at a clinical facility. Patients remained on their typical diet, and were not allowed to use any nutritional supplementation. They read and signed an informed consent form before participation in the study according to the Declaration of Helsinki. Patients that had any potential functional limitation or medical condition that could be aggravated by the tests were excluded. The study protocol was approved by the local ethics committee (CAE: 03498812.7.0000.5269). The inclusion criteria were: postmenopausal women with type 2 diabetes. Exclusion criteria included type 1 diabetes, daily insulin use, hormone replacement therapy and patients using 1000 d/u of Vitamin D continuously for more than 3 months.

2.2. Biochemical assays

The blood samples were collected after fasting for 12 h. Main outcome parameters were serum follicle-stimulating hormone (FSH) and estradiol were measured by enzyme-linked fluorescent assays (FSH: ref. 30407, estradiol II (E2II): ref. 30431, bioMérieux, Marcy-l'Etoile, France); 25-OH vitamin D was measured by chemiluminescent microparticle immunoassay (ref. 3L52G2-3231/R03, Abbott Diagnostics, Wiesbaden, Germany); insulin was measured by electrochemiluminescent immunoassay (ref. 1201547 122, Roche Diagnostics, Indianapolis, USA); and, C-Reactive Protein Gen.3 (CRP) was measured by immunoturbidimetry assay (ref. 05172373 190, Roche Diagnostics, Indianapolis, USA). Serum cholesterol total (CT), triglycerides (TG), high density lipoprotein (HDL-cholesterol), glucose and calcium were measured by colorimetric method (CT: ref. 864121022/01, TG: ref. 864126522/01, HDL-cholesterol: ref. 861265522/01, glucose: ref. 870560022/01, calcium: ref. 864120500/00, Wiener Laboratorios, Rosario, Argentina). All biochemical assays were performed according to the manufacturer's instructions.

The intra-assay and inter-assay coefficient of variation (% CV) were respectively: FSH = 4.2% CV and 4.7% CV; estradiol = 4.1% CV and 6.3% CV; 25-OH vitamin D = 3.1% CV and 4.0% CV; insulin = 1.5% CV and 3.7% CV; CRP = 1.5% CV and 2.4% CV; CT = 3.5% CV (intra-assay); TG = 0.33% CV (intra-assay); HDL-cholesterol = 1.7% CV and 2.4% CV; glucose = 1.9% CV (intra-assay); calcium = 1.4% CV and 1.0% CV.

HOMA-IR and HOMA-β indices were calculated as described by Diabetes Trial Unit (2008); low density lipoprotein (LDL-Cholesterol) were calculated by friedel formule.

2.3. Statistical analysis

Statistical analysis was initially performed using the Kolmogorov-Smirnov normality test. Student's *t*-test for normal samples and the Wilcoxon test for the non-normal samples were applied. The correlation between vitamin D status and other variables studied were assessed by Spearman coefficient. The level of significance was set at $p < 0.05$. All statistical analyses were carried out using GraphPad Prism statistical software package 5.0 version (GraphPad Software, Inc.; La Jolla, CA, USA). All data are reported as means and standard deviation (SD).

3. Results

The average serum 25(OH)D level in this study was 28.45 ± 8.26 ng/mL. The prevalence of hypovitaminosis D was 60%. Table 1 displays mean and standard deviation values for participants' characteristics. The postmenopause status of the women studied was confirmed by FSH and estradiol measurement.

All the clinical and anthropometric characteristics did not show difference ($p > 0.05$) between the groups (Table 2). Triglycerides level was highest ($p < 0.0391$) in the hypovitaminosis D group. The other serum markers did not show statistical differences ($p > 0.05$) between the groups (Table 3 and Table 4).

4. Discussion

In this study was found frequency of 60% of hypovitaminosis D (i.e. serum 25(OH)D < 30 ng/mL) in postmenopausal women with

Table 1
Participants' characteristcs (n = 70).

Characteristics	Total (n = 70)
Age (years)	59.47 ± 6.47
Weight (Kg)	73.56 ± 13.01
Height (m)	1.56 ± 0.05
Age of menopause (years)	47.87 ± 4.89
Menopause time (years)	11.54 ± 7.75
Body mass index Kg/m^2	30.30 ± 5.00
Waist circumference (cm)	99.39 ± 11.76
Insulin (mcU/mL)	11.50 ± 14.60
Follicle stimulating hormone (mUI/mL)	52.64 ± 18.56
Estradiol (pg/mL)	25.43 ± 27.62
Fasting glucose (mg/dL)	133.29 ± 50.14
25(OH)D (ng/mL)	28.45 ± 8.26
Total Cholesterol (mg/dL)	193.33 ± 34.41
LDL- Cholesterol (mg/dL)	110.11 ± 30.13
HDL- Cholesterol (mg/dL)	49.13 ± 10.36
Triglycerides (mg/dL)	170.44 ± 85.25
Calcium (g/dL)	9.94 ± 1.32
C-reactive protein (mg/dL)	0.53 ± 0.47
HOMA-IR	3.78 ± 5.82
HOMA-β	68.38 ± 63.10

Data are presented as mean ± standard deviation (SD). LDL: low density lipoprotein; HDL:high density lipoprotein; HOMA-IR: homeostasis model assessment-estimated insulin resistance; HOMA-β: homeostasis model assessment-estimated beta cell function.

Table 2
Clinical and anthropometric characteristics between vitamin D normal level group and hypovitaminosis D group.

Characteristics	Vitamin D normal level group (≥30 ng/mL) (N = 28)	Hypovitaminosis D group (<30 ng/mL) (n = 42)	P Value
Age (years)	60.07 ± 6.46	59.05 ± 6.54	0.5261
Weight (Kg)	74.74 ± 12.82	72.73 ± 13.24	0.5346
Height (m)	1.56 ± 0.06	1.55 ± 0.05	0.5331
Age of menopause (years)	47.68 ± 4.77	48.00 ± 5.03	0.7919
Menopause time (years)	12.88 ± 8.12	10.97 ± 7.57	0.5549
Body mass index (Kg/m^2)	30.55 ± 4.24	30.12 ± 5.52	0.7323
Waist circumference (cm)	100.63 ± 11.26	98.53 ± 12.15	0.4716

Data are presented as mean ± standard deviation (SD).

Table 3
Serum markers related to glycemic profile of postmenopausal women with type 2 diabetes at vitamin D normal level group and hypovitaminosis D group.

Characteristics	Vitamin D normal level group (≥30 ng/mL) (N = 28)	Hypovitaminosis D group (<30 ng/mL) (n = 42)	P Value
Insulin (mcU/mL)	9.51 ± 7.93	12.93 ± 17.93	0.4200
Follicle stimulating hormone (mUI/mL)	47.78 ± 19.57	55.87 ± 17.34	0.0738
Estradiol (pg/mL)	28.92 ± 28.29	23.08 ± 27.31	0.4215
Fasting glucose (mg/dL)	131.04 ± 53.54	134.79 ± 48.35	0.7617
Total Cholesterol (mg/dL)	184.86 ± 31.27	198.98 ± 35.59	0.0928
LDL- Cholesterol (mg/dL)	105.43 ± 25.55	113.23 ± 32.76	0.2917
HDL- Cholesterol (mg/dL)	50.46 ± 11.13	48.24 ± 9.85	0.3823
Triglycerides (mg/dL)	144.82 ± 53.41[a]	187.52 ± 98.00[b]	0.0391*
Calcium (g/dL)	10.15 ± 0.56	9.80 ± 1.64	0.2793
C-reactive protein (mg/dL)	0.53 ± 0.34	0.53 ± 0.52	0.9636
HOMA-IR	2.96 ± 2.64	4.35 ± 7.21	0.3355
HOMA-β	64.05 ± 51.25	71.33 ± 78.53	0.6414

Data are presented as mean ± standard deviation (SD). HOMA-IR: homeostasis model assessment-estimated insulin resistance; HOMA-β: homeostasis model assessment-estimated beta cell function. Within rows, values with different letters indicate significant differences ($p < 0.05$) between the groups. *t-test.

Table 4
Correlation between vitamin D status with clinical and anthropometric characteristics and serum markers.

Characteristics	R-Value	P-Value	95% Confidence Interval
Body mass index (Kg/m^2)	0,01004	0,9352	Lower −0.2358 Upper 0.2547
Waist circumference (cm)	0,02751	0,8238	Lower −0.2192 Upper 0.2709
Insulin (mcU/mL)	−0,1814	0,1358	Lower −0.4069 Upper 0.06493
Fasting glucose (mg/dL)	0,04182	0,7311	Lower −0.2019 Upper 0.2807
Total Cholesterol (mg/dL)	−0,1904	0,1144	Lower −0.4131 Upper 0.05379
LDL- Cholesterol (mg/dL)	−0,07181	0,5547	Lower −0.3082 Upper 0.1729
HDL- Cholesterol (mg/dL)	0,1118	0,3569	Lower −0.1335 Upper 0.3442
Triglycerides (mg/dL)	−0,3068	0,0098[a]	Lower −0.5107 Upper −0.07036
Calcium (g/dL)	−0,06553	0,5899	Lower −0.3024 Upper 0.1790
C-reactive protein (mg/dL)	−0,04296	0,7259	Lower −0.2835 Upper 0.2026
HOMA-IR	−0,1312	0,2824	Lower −0.3631 Upper 0.1159
HOMA-β	−0,1640	0,1781	Lower −0.3918 Upper 0.08274

[a] Correlation is significant at the 0,05 level.

type 2 diabetes. This result was similar with other studies also carried out in sunny cities. Russo et al. showed a frequency of 68,3% of hypovitaminosis D in postmenopausal women living in city of Rio de Janeiro during the winter months. Bandeira et al. showed a frequency of 43,7% of hypovitaminosis in postmenopausal women living in city of Recife.

Body mass index (Kg/m^2) and waist circumference (cm) were not different between the hypovitaminosis D group and vitamin D normal level group. These anthropometric measurements also did not show association with vitamin status, however, Griz [9] showed an inverse association between vitamin D status and BMI. He describe that obesity would be directly associated with hypovitaminosis D because this vitamin is a fat soluble compounds and may be retained in adipose tissue, which makes it less bioavailable.

The insulin, glucose, HOMA-IR and HOMA-β were not different when compared hypovitaminosis D group and vitamin D normal level group and, did not show association with vitamin D status. Boucher et al. [10] (1995), Malabanan et al. [11] and Wei et al. [12] described an association a positive association between vitamin D status and insulin sensibility. Pittas et al. [13] described that there is an improvement in the HOMA-IR index with calcium and vitamin D supplementation. The major mechanism of action of vitamin D in the synthesis and secretion of insulin probably involves β cells with calcium-dependent enzymes, which facilitate the conversion of proinsulin into insulin [14,15].

CRP has been used since the 1970s to diagnose inflammatory conditions and infections. The negative correlation has been described between serum levels of 25(OH)D and C-reactive protein (CRP) [16–18]. In our study the CRP did not show difference between hypovitaminosis D group and vitamin D normal level group and also did not show association with vitamin D status [18].

The CT, HDL-cholesterol, LDL-cholesterol and calcium were not different ($p > 0,05$) when compared hypovitaminosis D and vitamin D normal level groups. These parameters also did not show association ($p > 0,05$) with vitamin D status. The TG level was highest ($p < 0,0391$) in the hypovitaminosis D group and it showed a negative correlation with vitamin D status. Christakos et al. [19] reported a positive association between calcium absorption and TGs synthesis. As vitamin D improves calcium absorption, it was expected that triglyceride levels were higher in patients with normal vitamin D levels than women with hypovitaminosis D [20].

In conclusion, our results suggest that only TG level shows a negative correlation with vitamin D status in postmenopausal

women with type 2 diabetes.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.03.040.

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