ABCS HEALTH SCIENCES

ORIGINAL ARTICLE

OPEN ACCESS

The importance of optimal 25-hydroxyvitamin D levels in the glycemic control of older adults with type 2 Diabetes Mellitus: Data from the study on aging and longevity EELO

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ABSTRACT

Introduction: Optimal serum levels of vitamin D are of great importance, especially in populations with comorbidities such as Diabetes Mellitus (DM). **Objective:** The study evaluated the relationship between hypovitaminosis D and glycemic control in older adults with type 2 DM. **Methods:** Cross-sectional and prospective study, part of the EELO project (Study on Aging and Longevity), conducted in Southern Brazil. Glycated hemoglobin (diabetes ≥6.5%) and serum levels of vitamin D (25(OH)D) were evaluated. Hypovitaminosis D was determined using cutoff points <20 and <30 ng/mL). Multivariate logistic regression was used to assess the risk of having uncontrolled DM. **Results:** Of the 120 older adults included in the study, aged between 60 and 87 years, 74.2% were women, 66.7% used hypoglycemic medications and 75.8% exhibited uncontrolled diabetes. An inverse correlation was observed between the levels of 25(OH) D and glycated hemoglobin (rS=-0.19, p=0.037), suggesting that low levels of vitamin D are associated with poor glycemic control in diabetic individuals. The prevalence of hypovitaminosis D when using the cutoff points of <20 and <30 ng/mL were 34.2% and 75.0%, respectively. The odds ratio (OR) analysis showed that individuals with 25(OH)D<20ng/mL have almost 4 times more risk of having uncontrolled DM (OR:3.94; CI95%:1.25-12.46, p=0.02) when compared to the older adults with sufficient levels of vitamin D. **Conclusion:** The results indicate that the optimal serum levels currently recommended for 25(OH)D should preferably be 30 ng/mL or higher to contribute to better glycemic control in older adults with type 2 DM.

Keywords: Vitamin D; 25-hydroxyvitamin D 2; aged; Diabetes Mellitus; Glycated hemoglobin A.

How to cite this article: Okuyama et al. The importance of optimal 25-hydroxyvitamin D levels in the glycemic control of older adults with type 2 Diabetes Mellitus: Data from the study on aging and longevity EELO. ABCS Health Sci. 2022;47:e022222 https://doi.org/10.7322/abcshs.2020128.1583

Received: Aug 14, 2020
Revised: Dec 31, 2020
Approved: Apr 26, 2021

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Declaration of interests: nothing to declare

INTRODUCTION

Hypovitaminosis D is defined as when there is an insufficiency or deficiency of circulating vitamin D (25(OH)D) and it may be associated with various comorbidities other than musculoskeletal disorders such as Diabetes Mellitus (DM), hypertension, cancer, immune diseases, and multiple sclerosis[1-3]. Several studies are currently underway to better elucidate how hypovitaminosis D may influence some diseases[1,4]. In what concerns type 2 DM, despite extensive research on vitamin D mechanisms, it is still unclear how it modulates or interferes in DM, but it is believed to act by increasing insulin secretion in pancreatic beta cells[5]. Moreover, in animal models, $1,25(OH)_2D3$, the active form of vitamin D, has been shown to up-regulate Glucose transporter 4 (GLUT4) translocation to the muscle cells and adipocytes surface which enhances glucose uptake and its intracellular utilization[6-8].

Other recent studies show that hypovitaminosis D may be an aggravating element in the DM pathophysiology from young to older adult populations[9]. The association between vitamin D deficiency and type 2 DM was strengthened when vitamin D receptor (VDR) and the enzyme 1-alpha hydroxylase, which converts 25(OH)D into the biologically active form 1,25-di hydroxyvitamin D, were found present and expressed in pancreatic beta cells[4]. Furthermore, vitamin D can also perform a role in insulin resistance and insulin secretion through immune and inflammatory system modulation, which are related to DM pathogenesis. Type 2 DM has already been associated with an increase in the levels of tumor necrosis factor-alpha beta, as well as C-reactive protein, plasminogen activation factor, and, interleukin-6[10]. Therefore, vitamin D may be an important component for better glycemic control in type 2 DM.

It is known that maintaining good glycemic control for individuals with diabetes prevents many complications[11]. Studies show that vitamin D supplementation may be effective in preventing certain diseases and sufficient vitamin D levels are a protective factor, such as against type 2 DM in postmenopausal women[12,13]. Oral vitamin D supplementation with daily doses of more than 2000 IU/day and for a short period (less than 3 months) has shown good effects in glycemic control of type 2 diabetes patients[14]. Thus, studies on the prevalence of hypovitaminosis D and the influence of vitamin D on DM in different population groups are needed to better understand and establish their possible association. This is even more necessary in populations at risk for hypovitaminosis D and DM, such as the aging people.

In recent decades, interest in vitamin D has increased not only in the knowledge of its benefits but also for the high prevalence of hypovitaminosis D worldwide[2,15]. Similarly, diabetes is a world health problem, with very significant increasing numbers over the last two decades, in which people living with diabetes tripled, especially in developed and developing countries[16].

Thus, the present study aimed to assess optimal serum levels of vitamin D and the potential relationship between hypovitaminosis D and glycemic control in older adults with type 2 DM.

METHODS

Design and study population

This is a cross-sectional and prospective study, part of the EELO (Study on Aging and Longevity) project, thematic and interdisciplinary research, conducted by the University of Northern Paraná (UNOPAR), city of Londrina, Brazil. EELO project aimed to evaluate the social-demographic and health indicators of the older adults population (60 years or older according to the World Health Organization for developing countries), through an epidemiological survey[17]. Out of 43.610 (12% of the city's total population), participants (n=519) were randomly selected from the community outpatient public health system and recruited to cover all five urban regions. Data were collected from June 2009 to December 2010. The main inclusion criteria were individuals 60 years or older, of both sexes, and physically independent according to stages 3 (low exercise capacity and sedentary) and 4 (average exercise capacity and physically active) Spirduso classification[18].

The exclusion criteria were older adults with chronic kidney (Estimated Glomerular Filtration Rate (eGFR) <60 mL/min per $1.73m^2$) (CKD-EPI equation)[19] or liver (serum levels of glutamic-oxaloacetic transaminase (AST) >40 IU/L, serum glutamic pyruvic transaminase (ALT) >50 IU/L for men and >35 IU/L for women, or AST/ALT ratio >2) disease and vitamin D supplementation, according to the self-report and the questionnaire of medications in use.

Biochemical assays

Blood samples obtained from each older adult after an average of 10-hour fasting were treated differently to achieve the requirements for each analysis. For serum and fluorinated plasma, samples were centrifugated for 10 minutes at 3000 rpm using a clinical centrifuge at room temperature (Laborline©2019 Elektra Vector Inverter System, Lapa, SP, Brazil).

To analyze Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), and creatinine, serum samples were processed through enzymatic or kinetics-colorimetric methods, respectively, in the automated analyzer AU400® Chemistry Analyzer (Beckman Coulter®, Indianapolis, IN, US), using Beckman Coulter® kits and control reagents. Fluorinated plasma was used for fasting glucose and processed by an automated enzymatic-colorimetric method (AU400® Chemistry Analyzer, Beckman Coulter® kit). Assay sensitivity, intra-assay and inter-assay coefficient of variation (% CV) were respectively: AST/ALT= 0.19 mAbsorbance at 340/380nm per minute for 1U/L, <5% CV and <10% CV; creatinine = 12.5 mAbsorbance at 520/800nm for

1 mg/dL, <3% CV and <6% CV; glucose = 2.0 mAbsorbance at 340/380nm for 1 mg/dL, <3% CV and <3% CV.

Whole blood EDTA was used to analyze HbA1c by High Liquid Performance Chromatography (HPLC) at D-10 Hemoglobin Testing System and reagent packs (Bio-Rad© Laboratories, Hercules, CA, US). Bio-Rad© D-10 Hemoglobin-A1c Program is certified by the National Glycohemoglobin Standardization Program (NGSP) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)[20]. Assay linearity, intra-assay and inter-assay coefficient of variation (% CV) were respectively: 3.8% to 18.5% HbA1c, 0.46 to 0.79% CV and 0.52 to 0.53% CV.

Vitamin D (25(OH)D) was measured using serum by automated chemiluminescence (Architect iSR2000 – Abbott© Diagnostics, Lake Forest, IL, US). This chemiluminescent microparticle immunoassay (CMIA) determines 25(OH)D2 and D3 in human serum in the range of 0-160 ng/mL[21]. This assay is Vitamin D Standardization Program (VDSP) certified and meets the precision performance criteria (total CV ≤10%) and accuracy (mean bias ≤5%)[22].

Classification of diabetes and hypovitaminosis D

To classify the studied population into proper diabetes status, the results of fasting glucose and glycated hemoglobin (HbA1c), the self-report on diabetes, and the use of hypoglycemic medications were assessed simultaneously. HbA1c was the major laboratory marker used to indicate both diabetes diagnosis and glycemic control due to its low biological variability and because it is not affected by acute stress. Since 2010, HbA1c has been recommended for diagnostic purposes as well as for treatment follow-up, once it predicts the patient's medium estimated glucose for the last three months, in contrast to the fasting glucose, which expresses an isolated and more recent glucose level[23]. Figure 1 shows the classification criteria for HbA1c levels and respective diabetes statuses.

The vitamin D status classification is considered the international guidelines and the Brazilian medical society Consensus[24], which recommends 25(OH)D serum levels ≥30 ng/mL for older adults (≥60 years old). Results <30 ng/mL were classified as hypovitaminosis D. In addition, to analyze the data from a further perspective, a second classification for hypovitaminosis D was performed using a <20 ng/mL cutoff, based on the recommendation currently applied for adults below 60 years of age, as shown in Figure 1.

Diabetes classification	HbA1c (%)
Non-diabetic	4.0 to 6.0
Pre-diabetic	5.7 to 6.4
Controlled diabetic	6.5 to 6.9
Uncontrolled diabetic	≥7.0
Vitamin D classification	**25(OH)D**
Normal (adult)	≥20 ng/mL
Hypovitaminosis (adult)	<20 ng/mL
Normal (older adult)	≥30 ng/mL
Hypovitaminosis D (older adult)	<30 ng/mL

Older adult: ≥60 years old; adult: <60 years old.[20,21]

Figure 1: Classification criteria for diabetes and vitamin D status according to the Guidelines of the Brazilian Society of Diabetes (SBD 2019–2020) and the Brazilian Society of Endocrinology and Metabolism (SBEM).

Statistical analysis

Descriptive statistics were used to present the demographic data from the study sample. Spearman test was applied to correlate HbA1c and vitamin D results. Statistical Package for Social Sciences version 15.0 (SPSS, London, UK) was used to perform a Binary Logistic regression to assess the risk to have uncontrolled Diabetes Mellitus in a multivariate analysis. The model included the following variables: age, sex, use of hypoglycemic medications, and the presence of hypovitaminosis D.

Ethics

The EELO project complies with the Declaration of Helsinki and was developed following the research ethical criteria involving human beings, and approved by the Research Ethics Committee of UNOPAR University (registered number: PP/0070/09). All participants signed a free and informed consent form authorizing laboratory analysis and the use of information for research purposes. Illiterate that participants agreed to participate by inserting fingerprints on the consent form.

RESULTS

In the present study, 519 participants were selected. However, 29 participants (7 below 60 years, 3 classified as physically dependent, 11 that did not collect all the samples required, and 8 under vitamin D supplementation), 17 older adults with alterations in liver functions, 122 older adults with kidney dysfunctions and 231 non-diabetic older adults were excluded. Thus, 120 individuals remained in this study for statistical analysis as presented in Figure 2.

Demographic characteristics are presented in Table 1. Older adults below 70 years of age represented 61.7% (n=74), and 74.2% (n=89) of the population sample were women. A great number of the participants (66.7%; n=80) were in use of hypoglycemic medications, and 75.8% (n=91) presented uncontrolled diabetes (those with HbA1c ≥7.0% under diabetic treatment or not). The range of 25(OH)D serum concentrations in the diabetic study population varied from 5.9 to 78.1 ng/mL (mean concentration ± SD: 25.2±9.6 ng/mL). Of the 120 included individuals, the prevalence of hypovitaminosis D was 75.0% (n=91), considering the 25(OH)D cutoff point of <30 ng/mL, applied for adults 60 years or older. Additionally, almost half of the older adults evaluated had 25(OH)D levels between 20 and 30 ng/

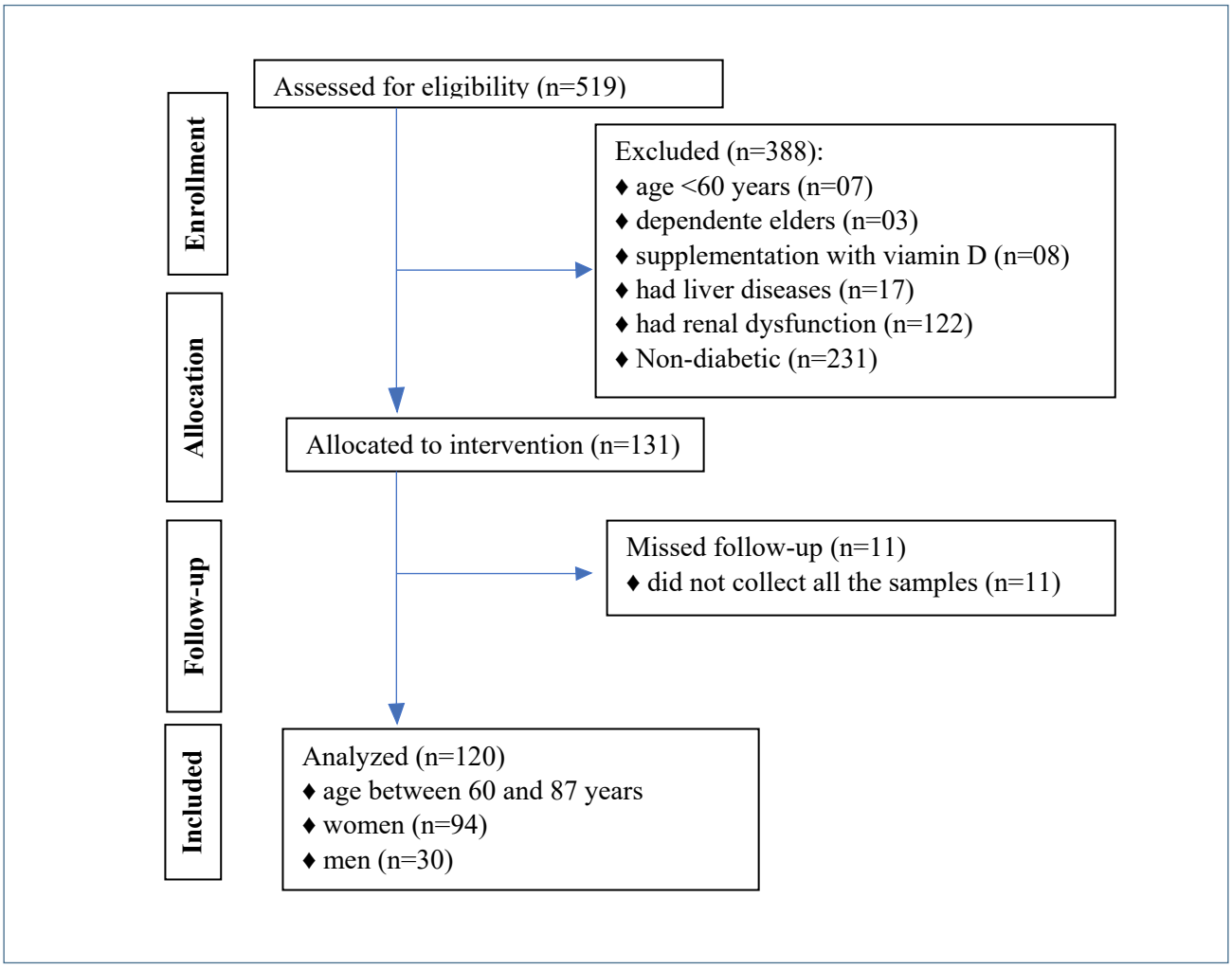

Figure 2: Selection flowchart of the population included in the study.

mL (45.8%; n=55), which indicates the importance of studying older adults populations in these results range.

Relationship between hypovitaminosis D and DM

An inverse correlation was observed between vitamin D (25(OH)D) levels and glycated hemoglobin according to the Spearman Correlation test (rS=-0.19, p=0.037), indicating that a lower level of vitamin D is associated with a worse glycemic control in diabetic patients, data shown in Figure 3.

Regarding the relation between hypovitaminosis D and poor glycemic control in diabetic older adults, it may be observed that only 9.8% of the individuals with low vitamin D have a controlled DM status, using the 20 ng/mL as the cutoff point. On the other hand, a controlled DM status was observed in 31.6% of the individuals with no hypovitaminosis D (Exact Fisher Test, p=0.007, Table 2). However, if we consider the cutoff point of 30ng/mL, no association was observed between the hypovitaminosis D and the glycemic control in diabetic older adults (Exact Fisher Test, p=0.22, Table 2).

When the cutoff point of 20 ng/mL was used to classify vitamin D status, at bivariate analysis, it was observed that age (p=0.17) and the presence of hypovitaminosis D (p=0.01) were associated

Table 1: Demographic characteristics of the study population.

Characteristics		n (%)
Sex	Male	31 (25.8)
	Female	89 (74.2)
Age (years)	<70	74 (61.7)
	≥70	46 (38.3)
Hypoglycemic medication	Yes	80 (66.7)
	No	40 (33.3)
Diabetes mellitus	Controlled	29 (24.2)
	Uncontrolled	91 (75.8)
Hypovitaminosis D (25(OH)D <20 ng/mL)	Yes	41 (34.2)
	No	79 (65.8)
Hypovitaminosis D (25(OH)D <30 ng/mL)	Yes	90 (75.0)
	No	30 (25.0)

with uncontrolled DM. On the other hand, sex (p=0.46) and the use of hypoglycemic medications (p=0.88) were not associated with uncontrolled DM. In the multivariate analysis, it was noticed that individuals with hypovitaminosis D have approximately 4 times more risk of having uncontrolled DM (OR:3.94; IC95%:1.25–12.46, p=0.02) when compared to individuals with normal vitamin D levels, after controlling age, sex and the use of hypoglycemic medications. No association between other predictors and uncontrolled DM was verified and these data are shown in Table 3.

When the cutoff point of 30ng/mL was used to classify vitamin D, at bivariate analysis, it was observed that age (p=0.17) and the presence of hypovitaminosis D (p=0.18) were associated with uncontrolled DM. On the other hand, sex (p=0.46) and the use of hypoglycemic medications (p=0.88) were not associated with uncontrolled DM. In the multivariate analysis, no predictors were associated with uncontrolled DM and these data are shown in Table 4.

DISCUSSION

Of the overall participants, women were the majority in the study population and the use of hypoglycemic medication and uncontrolled diabetes prevailed among the older adults. The higher prevalence of women than men in older populations is evidenced worldwide, as the declines in mortality rates are consistently greater for women and they have higher life expectancy[25]. In Brazil, the proportion of men to women 60 years or older by the year 2020 was estimated at 79 to 100[26]. Though, regardless of sex, glycemic control in older adults is a challenge, since aggressive glucose control and hypoglycemia may be a cause of harm in this population. The American Diabetes Association and the Brazilian

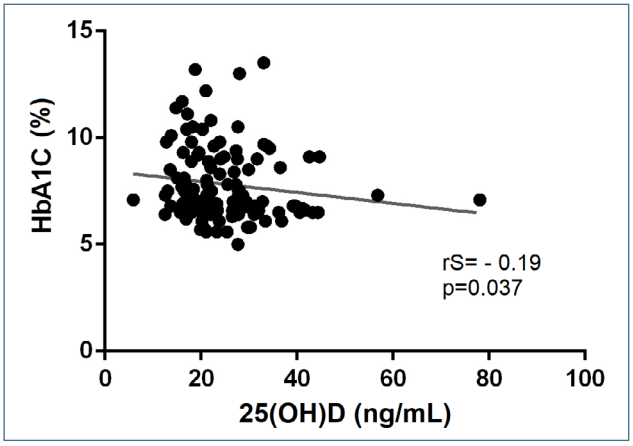

Figure 3: Spearman correlation (r) for HbA1c and 25(OH)D for the overall diabetic older adults included in the study (rS=-0.19, p=0.037).

Table 2: Descriptive data that shows the presence of hypovitaminosis D (20 and 30ng/mL as the cutoff points) and the glycemic control in diabetic older adults.

Hypovitaminosis D	Diabetes mellitus		Total
	Controlled	Uncontrolled	
25(OH)D <20 ng/mL	n (%)	n (%)	n (%)
Yes	4 (9.8%)	37 (90.2%)	41 (100%)
No	25 (31.6%)	54 (68.4%)	79 (100%)
Total	29 (24.2%)	91 (75.8%)	120 (100%)
25(OH)D <30 ng/mL			
Yes	19 (21.1%)	71 (78.9%)	90 (100%)
No	10 (33.3%)	20 (66.7%)	30 (100%)
Total	29 (24.2%)	91 (75.8%)	120 (100%)

Table 3: Relation between predictor variables and the outcome of *uncontrolled DM* (bivariate and multivariate analysis – Binary Logistic Regression) in older adults, for hypovitaminosis D (25(OH)D <20 ng/mL).

Variables	Bivariate Analysis				Multivariate Analysis			
	OR	CI 95%	Wald	p	OR	CI 95%	Wald	p
Age								
<70 years old	1.0	-	1.83	0.17	1.0	-	0.65	0.42
>70 years old	1.88	0.75–4.69			1.6	0.50–5.17		
Sex								
Male	1.0	-	0.54	0.46	-	-	-	-
Female	0.71	0.28–1.78			-	-		
Hypoglycemic medications								
Yes	1.0	-	0.02	0.88	-	-	-	-
No	1.07	0.44–2.58			-	-		
Hypovitaminosis D (25(OH)D < 20ng/mL)								
Yes	4.28	1.37–13.3	6.30	0.01	3.94	1.25–12.46	5.45	0.02*
No	1.0	-			1.0	-		

CI: confidence interval, OR: odds ratio, Wald: Wald test, *p<0.05 was considered significant.

Table 4: Relation between predictor variables and the outcome of *uncontrolled DM* (bivariate and multivariate analysis – Binary Logistic Regression) in older adults, for hypovitaminosis D (25(OH)D<30ng/mL).

Variables	Bivariate Analysis				Multivariate Analysis			
	OR	CI 95%	Wald	p	OR	CI 95%	Wald	p
Age								
<70 years old	1.0	-	1.83	0.17	1.0	-	1.67	0.19
>70 years old	1.88	0.75–4.69			1.83	0.73–4.61		
Sex								
Male	1.0	-	0.54	0.46	-	-	-	
Female	0.71	0.28–1.78			-	-		
Hypoglycemic medications								
Yes	1.0	-	0.02	0.88	-	-	-	-
No	1.07	0.44–2.58			-	-		
Hypovitaminosis D (25(OH)D<30 ng/mL)								
Yes	1.87	0.75–4.65	1.80	0.18	1.81	0.72–4.55	1.61	0.20
No	1.0	-			1.0	-		

CI: confidence interval, OR: odds ratio, Wald: Wald test, *p<0.05 was considered significant.

Society of Diabetes recommend individualized glycemic control. Sometimes, less rigorous in the elderly population, depending on specific conditions, such as impairment in cognition and physical function, besides other associated medical issues[23,27]. For this study, uncontrolled diabetes was considered for those participants exhibiting HbA1c ≥7.0%, the main follow-up target for adults under diabetic treatment.

The results found in this study showed that the number of older adults with hypovitaminosis D doubled when using <30 ng/mL cutoff for 25(OH)D, in comparison to the prevalence of hypovitaminosis D when the cutoff applied, was <20 ng/mL, and that the great part of participants exhibited 25(OH)D levels between 20 and 30 ng/mL (45.8%; n=55). This result indicates that almost half of these older adults presented vitamin D in this critical range, below the recommended threshold. A similar concern was evidenced in the Third International Conference on Controversies in Vitamin D, held in September 2019, in which the thresholds for vitamin D deficiency were debated. Although there is a consensus for 25(OH)D levels below 12 ng/mL (deficiency at all ages) and above 30 ng/mL (as sufficient), disagreement remains for the values ranging between 12 and 30 ng/mL[28]. Hypovitaminosis D may influence the reduction of glucose tolerance and impairment of insulin secretion, leading to the development of type 2 DM. The mechanism involved in this finding is possibly related to the expression of VDR in several cells and tissues[4]. Thus, changes in the endocrine system because of variations in VDR expression and low levels of vitamin D can affect insulin secretion and insulin sensitivity[29,30].

Present investigation demonstrated an inverse correlation between 25(OH)D and HbA1c levels in the diabetic older adults group, which was statistically significant (rS=-0.19, p=0.037). These results corroborate with the study carried out by Zoppini et al.[31], with 715 types 2 DM patients, in which they showed that HbA1c and vitamin D were inversely related (r=-0.116, p=0.003). Kajbaf et al.[32] also demonstrated this inverse relation between vitamin D and HbA1c levels (r=−0.387, p<0.0001) in 245 individuals with an average age of 65 years old. Although these correlations are significant, they do not express strong association results. The inconclusiveness of some research focused on the correlation of 25(OH) vitamin D deficiency with HbA1C and the benefit of its supplementation to prevent type 2 DM could be due to the absence of concomitant VDR analysis. Even though not elucidated, VDR gene polymorphisms and expressions have been associated with diabetes. Recently, it has been suggested that glucose can modulate the VDR expression in pancreatic β-cells in healthy mice models and that its overexpression reduces inflammation, which may be a protective element against diabetes[33].

In the current study, data analysis of older adults with 25(OH)D serum levels <30 ng/mL, showed no difference in the prevalence of hypovitaminosis D between the groups with or without DM2. Nevertheless, when hypovitaminosis D is classified by lower levels of 25(OH)D (<20 ng/mL), the risk of uncontrolled diabetes is approximately four times higher compared to individuals with normal levels of vitamin D. The Odds ratio value obtained in this analysis expresses a big effect size for hypovitaminosis and substantial clinical relevance[34]. Similar results were also observed by Kostoglou-Athanassiou et al.[35], in which type 2 DM patients presented lower levels of vitamin D. According to the 1st International Conference on Controversies in Vitamin D, levels of 25(OH)D above 20 ng/mL are considered as sufficient for the general population[36,37]. Nevertheless, the Brazilian medical societies Consensus has established that levels of 25(OH)D should be ≥30 ng/mL for people at risk, such as the older adults[24]. Corroborating with that guideline, the results presented in this study suggest that

it is important to keep 25(OH)D levels above 30 ng/mL in older adults with type 2 DM, to obtain better glycemic control.

In a case-control study with 2000 young adults, divided into two groups (1,000 with DM and 1,000 healthy controls), it was observed that individuals with lower levels of vitamin D had a higher risk for insulin-requiring diabetes and that individuals with serum levels of 25(OH)D ≥60 nmol/L (approximately 24 ng/mL) had 3.5 times lower risk[38]. However, other studies point to divergent results, such as in the study conducted by Lips et al.[1], in which a randomized clinical trial with vitamin D versus placebo in prediabetic and type 2 DM patients showed inconsistent conclusions. Another study has shown that vitamin D supplementation in patients with type 2 DM may improve levels of HbA1c and insulin resistance in short-term interventions, suggesting that vitamin D can be considered a therapeutic agent along with other treatments for type 2 DM[39]. In addition, Pittas et al.[40], upon performing a follow-up for two and a half years using vitamin D supplementation to verify whether its possible action in reducing type 2 DM, did not observe a protective role in individuals with sufficient vitamin D levels. Still, in individuals with vitamin D deficiency (12-19 ng/mL), significant results were observed.

Despite the associations found, this study has some limitations. Firstly, although it was possible to gather the information about the medications in use by the participants, the proper adherence to the treatment was not evaluated, and part of those who reported taking hypoglycemic medications might not be doing it accurately. Secondly, vitamin D results require further examination between the range of 20 and 29 ng/mL of 25(OH)D for a better understanding of the exact threshold that a higher risk for uncontrolled diabetes would occur. In that direction, a ROC curve was performed, but it was not possible to analyze the data due to the small sample for that analysis.

In conclusion, the data obtained in this study reinforce that the 25(OH)D optimal levels of 30ng/mL or higher, currently recommended, contribute to better glycemic control in older adults with type 2 DM.

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