Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

Vitamin D Status and Cardiovascular Risk Factors in Patients with Type 2 Diabetes Mellitus: A Cross-Sectional Study in a Tertiary-Level Hospital in Antananarivo, Madagascar

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Background: Diabetes mellitus is already a major cardiovascular risk factor (CRF). Hypovitaminosis D is common in patients with type 2 diabetes mellitus (T2DM). It also increases the cardiovascular risk of these subjects.

Objective: To determine the vitamin D status of Malagasy with T2DM seen at the Soavinandriana Hospital Center, and the association between hypovitaminosis D and CRF.

Methods: This was a cross-sectional study, carried out over a period of 2 years. Assayed by the chemiluminescence technique, vitamin D was "normal", "insufficient" and "deficient" if the 25-hydroxyvitamin D plasma was ≥30 ng/mL, 20–29 ng/mL and ≤19 ng/mL, respectively. Hypovitaminosis D was the set of vitamin D insufficiency and deficiency.

Results: Among the 318 T2DM, the prevalence of hypovitaminosis D was 66.0% (45.2% insufficiency and 20.8% deficiency). Their factors associated were age ≥70 years (OR = 2.15 [1.26–3.66]), glycated haemoglobin ≥7% (4.97 [2.97–8.39]), and retinopathy (OR = 4.15 [1.85–9.32]). After adjustment for age, Hb A1c ≥7% and retinopathy, hypovitaminosis D was associated with hypertension (OR = 8.77 [4.76–16.2]), dyslipidaemia (OR = 8.05 [3.98–14.5]), ex-smoking (OR = 6.07 [2.78–13.3]), microalbuminuria (OR = 2.95 [1.25–6.97]) and carotid atherosclerosis (OR = 2.96 [1.83–4.35]).

Conclusion: Hypovitaminosis D was common in T2DM. Its treatment is primarily preventive. It is also important to control associated CRF, diabetes and its complications.

Keywords: 25-hydroxyvitamin D, cardiovascular risk factors, hypovitaminosis D, Madagascar, type 2 diabetes mellitus

Introduction

Apart from phospho-calcium homeostasis,[1] vitamin D plays an important role in the progression of metabolic, auto-immune and cardiovascular pathologies.[2,3] In the general population, vitamin D deficiency is already a major public health problem in all age groups globally, even in countries exposed to the sun all year round.[4]

Particularly in patients with diabetes mellitus, vitamin D could interact with the different pathophysiological mechanisms governing insulin secretion, insulin resistance and parameters of carbohydrate homeostasis.[5,6] Thus, a vitamin D deficiency promotes the occurrence of diabetes and the imbalance of known diabetes.[7,8] It could also intervene in diabetes complications and all-cause mortality.[9,10] Meanwhile, patients with type 2 diabetes mellitus (T2DM) often have several cardiovascular risk factors (CRF) which are significantly associated with vitamin D deficiency and will further promote the occurrence of complications.[11]

To our knowledge, data on this subject are very scarce in Madagascar. We hypothesize that vitamin D deficiency is also common among Malagasy with T2DM and associated with other CRF. The present study was carried out with the

Received: 5 March 2024
Accepted: 28 May 2024
Published: 31 May 2024

objectives of determining the vitamin D status of Malagasy with T2DM seen at the Soavinandriana Hospital Center, and the association between hypovitaminosis D and CRF, in order to improve their care.

Materials and Methods

Study Design and Setting

This was a descriptive and analytical cross-sectional study, carried out in the Cardiovascular Diseases and Internal Medicine departments of the Soavinandriana Hospital Center (Military Hospital) in Antananarivo. These services are part of the references for the management of cardiovascular, internal medicine, metabolic and endocrine diseases in the capital and even the country (Madagascar). The study spanned a period of 2 years from January 2022 to December 2023.

Study Population

Our study population consists of out-patients with T2DM known for at least 1 year, benefiting from vitamin D measurement. The diagnosis of diabetes was based on the patient's declaration, the taking of an antidiabetic medication or the diagnostic criteria of the American Diabetes Association. T2DM was considered if the patient was over 35 years old, overweight or obesity, family history of type 2 diabetes, and the absence of obvious secondary causes (chronic pancreatitis, endocrinopathies, taking long-term glucocorticoid).[12] Patients with incomplete records were excluded from the study.

The sampling of the population was exhaustive. The sample size was determined using a single population proportion formula: n = (Z1-α/2)2 P (1-P)/d2); based on the assumptions of 95% confidence level (Z1-α/2 = 1.96), 5% margin of error and a 28% prevalence of vitamin D deficiency. The prevalence of 28% was taken because there was no similar study done in Madagascar previously. The final sample size for the study was 318 patients with T2DM who consented to participate.

Clinical and Laboratory Data

The variables studied were demographic data (age, gender), cardiovascular risk factors (hypertension, dyslipidaemia, smoking, overweight/obesity, microalbuminuria), diabetic disease (duration, treatment, glycated hemoglobin or Hb A1c, diabetic kidney disease, retinopathy, peripheral neuropathy, ischemic stroke, carotid atherosclerosis, ischemic heart disease, lower limb arteriopathy), vitamin D status (normal, deficiency, insufficiency).

The presence of hypertension was certified by blood pressure ≥140/90 mmHg (based on an average of ≥2 measurements obtained on ≥2 occasions) or taking antihypertensive medication. Patients with low-density lipoprotein cholesterol (LDLc) levels outside the targets recommended by the European Society of Cardiology[13] or taking a lipid-lowering agent were considered to have dyslipidaemia. The body mass index (BMI) was calculated as the weight in kilograms (kg) divided by the square of the height in meters (m²). Hb A1c was measured using the High-Performance Liquid Chromatography (HPLC) method. Diabetes was said to be uncontrolled if Hb A1c was ≥7%.

The microalbuminuria measurement was quantitative and carried out in the laboratory. The colorimetric assay on Alinity C 8502 made it possible to obtain the serum creatinine (µmol/L). The estimated glomerular filtration rate (eGFR) (mL/min/1.73 m²) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The diagnosis of diabetic kidney disease was confirmed in the presence of microalbuminuria ≥30 mg/24 hours and/or a reduction in eGFR <60 mL/min/1.73 m², in the absence of signs or symptoms of other primary causes of kidney damage, associated with long-term diabetes, with or without diabetic retinopathy.[14,15] Retinopathy is posed in the face of abnormalities in the examination of the vitreous and fundus after pupillary dilation.[16] Diabetic peripheral neuropathy is considered in the presence of symmetrical distal sensory symptoms beginning in the lower limbs assessed using the DN4 questionnaire and an alteration of the sensitivity of the foot on examination with a 10g monofilament and a reduction or absence of the Achilles reflex.[16,17] The diagnosis of ischemic stroke was considered in the face of focal neurological signs of sudden onset such as motor and/or sensory deficit and confirmed by parenchymal hypodensity corresponding to one or more affected arterial territories(s) on brain scan.[18] Carotid atherosclerosis was defined as the presence of carotid plaque or diffuse thickening of the carotid wall (≥1.1mm).[19] The diagnosis of ischemic heart disease is made based on the presence or absence of typical or atypical chest pain and/or other atypical signs, the Q wave of necrosis and negative T in one or more territories defined on the ECG, and segmental akinesia or hypokinesia on echocardiography.[20,21] Lower limb arteriopathy is confirmed by arterial Doppler ultrasound, whether in the form of stenosing atherosclerosis or not, or mediacalcosis.

The 25-hydroxyvitamin D plasma measurement is done by the chemiluminescence technique on Alinity i from Abbott 7710. According to the recommendations of the Endocrine Society, it is "normal", "insufficient" and "deficiency" if it was ≥30 ng/mL, 20–29 ng/mL and ≤19 ng/mL, respectively.[22] Hypovitaminosis D is the set of vitamin D insufficiency and deficiency.

Statistical Analysis

Data was collected from a pre-established survey form from patient medical records. Then, they were used using Epi Info™ version 3.5.4 software (United States Centers for Disease Control and Prevention in Atlanta, Georgia). Qualitative and quantitative variables were, respectively, expressed as proportion and median with interquartile range [25% and 75%]. The chi-square test with a significance threshold less than 0.05 and the odds ratio (OR) was used to determine the factors associated with hypovitaminosis D. This OR is affected by a 95% confidence interval [95% CI].

Ethical Considerations

The study adhered to the principles outlined in the Declaration of Helsinki. Before carrying out the study, a request for authorization to collect data was sent and granted by the General Director of the hospital and the head of department. Patients' anonymity and confidentiality were respected. Review Board of Soavinandriana Hospital approved this study.

Results

Among the 318 patients with T2DM, 59% were women. Their median age of 65 years with [interquartile ranges (IQ): 60 years – 72 years]. The most frequent risk factors were hypertension and dyslipidaemia in 63.8% and 62.5% of cases, respectively. The median duration of progression of diabetes was 4 years [2 years – 8 years]. The median glycated hemoglobin was 8.2% [6.5%–13.6%]. Chronic degenerative complications were dominated by peripheral neuropathy and lower limb arteriopathy in 43.6% and 33.3% of cases, respectively. Table 1 shows the general characteristics of the study population.

Table 1 General Characteristics of the Study Population

Variables	Numbers	Percentage
Male gender	131	41.2
Age groups (year)		
[36–39]	25	7.9
[40–49]	18	5.6
[50–59]	34	10.7
[60–69]	137	43.1
≥70	104	32.7
Cardiovascular risk factors		
Hypertension	203	63.8
Dyslipidaemia	195	62.5
Overweight or obesity	141	44.3
Ex-smoking	98	30.8
Current smoking	25	7.9
Microalbuminuria	64	20.1

(*Continued*)

Table 1 (Continued).

Variables	Numbers	Percentage
Diabetes duration ≥5 years	154	48.4
Diabetes treatment		
Oral antidiabetics alone	178	56.0
Oral antidiabetics and insulin	65	20.4
Comprehensive lifestyle modification	51	16.0
Insulin alone	24	7.6
Diabetes complications		
Peripheral neuropathy	139	43.7
Retinopathy	72	22.6
Diabetic kidney diseases	65	20.4
Lower limb arteriopathy	52	33.3
Carotid atherosclerosis	89	28.0
Ischemic heart disease	65	20.4
Ischemic stroke	8	2.5

Mean vitamin D was 25.7 ± 6.8 ng/mL with extremes of 10 ng/mL and 37.4 ng/mL. The prevalence of hypovitaminosis D was 66.0%. Table 2 shows the distribution of patients according to their vitamin D status.

In multivariate analysis adjusted for age, the factors associated with hypovitaminosis D were Hb A1c ≥7% (OR = 5.08 [3.06–8.45]) and retinopathy (OR = 6.71 [2.95–1.23]). Table 3 summarizes the factors associated with hypovitaminosis D.

Adjusted for age, Hb A1c ≥7% and retinopathy, hypertension (OR = 8.77 [4.76–16.2]), dyslipidaemia (OR = 8.05 [3.98–14.5]), ex-smoking (OR = 6.07 [2.78–13.3]), microalbuminuria (OR = 2.95 [1.25–6.97]) and carotid atherosclerosis (OR = 2.96 [1.83–4.35]) were significantly associated with hypovitaminosis D (Table 4).

Discussion

Hypovitaminosis D (vitamin D deficiency and insufficiency) likely has multiple repercussions. It can be the cause of a public health problem because it is present in all categories of the population such as T2DM. In the present study, T2DM had vitamin D deficiency, insufficiency and normal vitamin D in 20.8%, 45.2% and 34.0% of cases, respectively. Among studies conducted in Africa, the prevalence of vitamin D insufficiency and deficiency varied from 14.4% to 46.0%, and from 38.4% to 78.0%, respectively.[23–25] A Chinese study showed that 42.2% of patients had vitamin D insufficiency and 31.6% had vitamin D deficiency.[26] In a study carried out in French Guiana, only 33.52% of diabetics had a normal vitamin.[27]

Table 2 Distribution of Patients According to Their Vitamin D Status

Variables	Numbers	Percentage
Vitamin D deficiency	66	20.8
Vitamin D insufficiency	144	45.2
Normal vitamin D	108	34.0

Table 3 Factors Associated with Hypovitaminosis D

Variables	Hypovitaminosis D		Bivariate Analysis		Multivariate Analysis	
	No (n1=108)	Yes (n2=210)	OR [95% CI]	p value	aOR [95% CI]	p value
Male gender, n (%)	42 (38.9)	89 (42.4)	1.15 [0.70–1.91]	0.2765		
Median age, years [IQ]	64 [52–68]	65 [60–74]		0.0001*		
Age groups, years						
[36–39], n (%)	17 (15.7)	8 (3.8)	0.21 [0.08–0.51]	0.0005*		
[40–49], n (%)	9 (8.3)	9 (4.3)	0.49 [0.19–1.27]	0.1460		
[50–59], n (%)	8 (15.4)	8 (7.7)	1 (reference)			
[60–69], n (%)	41 (38.0)	96 (45.7)	1.37 [0.84–2.28]	0.1144		
≥70, n (%)	24 (22.2)	80 (38.1)	2.15 [1.26–3.66]	0.0018*		
Median duration of diabetes, years	5 [2–8]	4 [2–8]		0.0738		
Duration of diabetes ≥ 5 years	58 (53.7)	96 (45.7)	0.73 [0.45–1.15]	0.1776		
Median Hb A1c, %	6.6 [6.1–8.4]	8.6 [7–10.1]		<0.0001*		
Hb A1c ≥7%, n (%)	42 (38.9)	161 (76.7)	5.13 [3.03–8.80]	<0.0001*	4.97 [2.97–8.39]	<0.0001*
Peripheral neuropathy, n (%)	42 (38.9)	97 (46.2)	1.34 [0.82–2.23]	0.1304		
Retinopathy, n (%)	8 (7.4)	64 (30.5)	5.45 [2.46–13.7]	<0.0001*	4.15 [1.85–9.32]	0.0006*
Diabetic kidney diseases, n (%)	25 (23.1)	40 (19.0)	0.78 [0.43–1.44]	0.2369		

Notes: *Statistically significant (p value <0.05).
Abbreviations: aOR, adjusted odds ratio; CI, Confidence Interval; Hb A1c, Glycated haemoglobin; IQ, Interquartile range; OR, odds ratio.

Table 4 Association Between Hypovitaminosis D, Cardiovascular Risk Factors and Macroangiopathies

Variables	Hypovitaminosis D		Bivariate Analysis		Multivariate Analysis	
	No (n1=108)	Yes (n2=210)	OR [95% CI]	p value	aOR [95% CI]	p value
Hypertension, n (%)	33 (30.6)	170 (81.0)	9.57 [5.47–17.1]	<0.0001*	8.77 [4.76–16.2]	<0.0001*
Dyslipidaemia, n (%)	29 (26.9)	166 (79.0)	9.08 [4.03–15.7]	<0.0001*	8.05 [3.98–14.5]	<0.0001*
Overweight or obesity, n (%)	60 (55.6)	81 (38.6)	0.50 [0.31–0.83]	0.0028*	0.45 [0.26–0.77]	0.0037*
Ex-smoking, n (%)	9 (8.3)	89 (42.4)	8.04 [3.79–19.1]	<0.0001*	6.07 [2.78–13.3]	<0.0001*
Current smoking, n (%)	0 (0)	25 (11.9)	NE	<0.0001*		
Microalbuminuria, n (%)	8 (7.4)	56 (26.7)	4.52 [2.03–11.5]	<0.0001*	2.95 [1.25–6.97]	0.0427*
Lower limb arteriopathy, n (%)	32 (29.6)	72 (34.3)	1.23 [0.73–2.12]	0.2390		
Carotid atherosclerosis, n (%)	16 (14.8)	73 (34.8)	3.05 [1.64–5.98]	<0.0001*	2.96 [1.83–4.35]	0.0325*
Ischemic heart disease, n (%)	25 (23.1)	40 (19.0)	0.78 [0.42–1.44]	0.2369		
Ischemic stroke, n (%)	0 (0)	8 (3.8)	NE	0.0345*		

Notes: *Statistically significant (p value <0.05).
Abbreviations: aOR, adjusted odds ratio; CI, Confidence Interval; NE, not estimable; OR, odds ratio.

This disparity could be linked to the difference in diagnostic criteria for hypovitaminosis D (vitamin D threshold value), the country of the study (little or very sunny), the population studied (skin pigmentation, customs, eating and clothing habits), and the season of blood sampling (winter, summer). In any case, hypovitaminosis D is very common in diabetes mellitus. However, screening and systematic vitamin D supplementation in patients with T2DM is still controversial by guidelines.[28]

In the present study, risk factors for hypovitaminosis D were age ≥70 years, Hb A1c ≥7% and retinopathy. Several studies have also shown that advanced age constitutes an independent risk factor for vitamin D deficiency.[25,29,30] Indeed, elderly subjects would have a more covering clothing habit and a short duration of exposure to the sun. In addition, skin synthesis of vitamin D under the effect of solar ultraviolet B rays is reduced with age. Thus, as age advances, screening for hypovitaminosis D should be strengthened. In other studies, glycemic imbalance was also significantly associated with hypovitaminosis D.[23,30] Lim et al had shown that each decrease of 10 nmol/L of vitamin D was significantly associated with an increase of 0.2% of glycated hemoglobin.[31] Therefore, screening for hypovitaminosis D should be reinforced in subjects with uncontrolled diabetes. Optimizing glycemic control could improve vitamin D status, and vice versa. Other authors had also found that retinopathy was significantly associated with a reduction in plasma vitamin D.[30,32] Thus, the presence of hypovitaminosis D could prompt the search for retinopathy, and vice versa. Furthermore, the role of gender in the occurrence of hypovitaminosis D remains disparate in the literature.[33,34]

In the present study, almost all classic CRFs (hypertension, dyslipidemia, smoking, microalbuminuria) were independent risk factors for hypovitaminosis D. This was also found by other authors.[30,35,36] Additionally, smoking decreases serum 25(OH)D and 1.25(OH)2D levels, dietary vitamin D intake, and skin vitamin D production through skin aging.[37] However, a clinical trial conducted by McMullan et al found no benefit to correcting vitamin D deficiency in blood pressure after 8 weeks.[38] In the present study, overweight/obesity was a protective factor for hypovitaminosis D (OR = 0.45 [0.26–0.77]). On the other hand, other authors have proven the opposite case, since weight affects the bioavailability of vitamin D through a sequestration effect of vitamin D in fat mass compartments.[30,31] According to the study by Rolim et al, hypovitaminosis D was correlated with high cholesterol and BMI values.[39] Regardless, early detection and adequate management of other associated CRFs still remain essential and could improve the vitamin D status of patients with T2DM. Vitamin D supplementation and increased sun exposure could reduce cardiovascular risk in patients with T2DM.

As for macrovascular complications, in the present study, only carotid atherosclerosis was significantly associated with hypovitaminosis D. Likewise in the study of Lupoli et al, both vitamin D deficiency and insufficiency are associated with subclinical atherosclerosis.[40] Hamdy Al-Said et al also found that hypovitaminosis in diabetic patients may be a risk factor for premature atherosclerosis assessed from the increase in intima-media thickness of the carotid artery in patients with T2DM.[41] An Italian study showed that hypovitaminosis D was independently associated with an increased prevalence and severity of coronary artery disease.[42] The roles of hypovitaminosis D in increasing the risk of cardiovascular diseases could be direct or indirect.[43] The pathophysiological pathways involved can be endothelial dysfunction, platelet aggregation, metabolic dysregulation and elevation of cellular and humoural inflammatory. Unfortunately, there is no clinical trial evidence on positive impact of vitamin D supplements on cardiovascular outcomes.[44,45]

The present study has limitations. Its retrospective nature did not make it possible to collect important information which was not included in all medical records, such as sun exposure and eating habits of the patients. Also due to the monocentricity of the study, the results we obtained cannot be extrapolated to the entire general diabetic population in Madagascar. A control group of non-diabetics was not available.

Conclusion

At the end of this study, hypovitaminosis D (deficiency and insufficiency) was common in patients with T2DM. It was significant at age ≥70 years, uncontrolled diabetes (Hb A1c ≥7%), complicated by retinopathy, carotid atherosclerosis and cardiovascular risk factors (dyslipidemia, hypertension, smoking and microalbuminuria). This study thus strengthens the importance of adequate management of associated cardiovascular risk factors, diabetes and its complications. It also calls for the development of clinical research protocols aimed at demonstrating the benefit of vitamin D supplementation in the treatment of T2DM, in order to achieve an effective strategy to combat this new "epidemic".

Disclosure

The authors report no conflicts of interest in this work.

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