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Vitamin D status and cardiovascular risk in individuals with metabolic syndrome

Status de vitamina D e risco cardiovascular em indivíduos com síndrome metabólica

Abstract

Introduction: Metabolic syndrome is a set of metabolic disorders that are considered cardiovascular risk factors. It is estimated that individuals with metabolic syndrome are three times more likely to develop cardiovascular disease. Inadequate vitamin D status has shown multiple pathophysiological mechanisms that suggest an involvement in the development of cardiovascular disease. ***Objective:*** To evaluate the association between vitamin D status and the risk of cardiovascular disease in individuals with metabolic syndrome. ***Methods:*** This is a cross-sectional study carried out with 161 adult individuals diagnosed with metabolic syndrome. Anthropometric measurements, blood pressure, and biochemical analyzes were performed, including serum 25(OH)D status. The established criterion for classifying 25(OH)D status was deficient < 20 ng/mL; insufficient ≤ 29 ng/mL and sufficient ≥ 30 ng/mL. Furthermore, the absolute risk of developing cardiovascular disease was assessed using the Framingham Risk Score. ***Results:*** The mean 25(OH)D concentration was 29.7 (21-34) ng/mL, indicating insufficient 25(OH)D status in the population. There was no association between vitamin D status and cardiovascular risk in subjects with metabolic syndrome ($p > 0.05$). ***Conclusion:*** There was no association between inadequate 25(OH)D status and increased cardiovascular risk in individuals with metabolic syndrome. However, these results reinforce the importance of clinical monitoring to prevent the impacts of hypovitaminosis D in individuals with metabolic syndrome and the development of new studies to assess the relationship between 25(OH)D status and cardiovascular risk.

Keywords: Metabolic Syndrome. Vitamin D. Cardiovascular Risk. Framingham Risk Score

Resumo

Introdução: A síndrome metabólica é um conjunto de desordens metabólicas, consideradas fatores de risco cardiovascular. Estima-se que indivíduos com síndrome metabólica apresentam probabilidade três vezes maior de desenvolver doenças cardiovasculares. O *status* inadequado de vitamina D tem apresentado múltiplos mecanismos fisiopatológicos que sugerem um envolvimento no desenvolvimento de doenças cardiovasculares. ***Objetivo:*** avaliar a associação entre o *status* de vitamina D e o risco de doenças cardiovasculares em indivíduos com síndrome metabólica. ***Métodos:*** Estudo do tipo transversal realizado com 161 indivíduos adultos, diagnosticados com síndrome metabólica. Foram realizadas as medidas antropométricas, pressão arterial, e as análises bioquímicas, incluindo a dosagem de 25(OH)D no soro. O critério estabelecido para classificação do *status* de 25(OH)D foi deficiente < 20 ng/mL; insuficiente≤ 29 ng/mL e suficiente ≥ 30 ng/mL. Ademais, avaliou-se o risco absoluto de desenvolver doenças cardiovasculares usando o Escore de Risco de Framingham. ***Resultados:*** A mediana da concentração de 25(OH)D foi 29,7 (21-34) ng/mL, indicando *status* de 25(OH)D insuficiente na população. Não houve associação entre *status* de vitamina D e o risco cardiovascular em indivíduos com síndrome metabólica ($p > 0,05$). ***Conclusão:*** Não se observou associação

entre *status* 25(OH)D inadequado e maior risco cardiovascular nos indivíduos com síndrome metabólica. Entretanto,esses resultados reforçam a importância do monitoramento clínico para prevenir os impactos da hipovitaminose D nos indivíduos com síndrome metabólica e o desenvolvimento de novos estudos para avaliar a relação entre *status* de 25(OH)D e risco cardiovascular.

Palavras-chave: Síndrome Metabólica. Vitamina D. Risco Cardiovascular. Escore de Framingham.

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INTRODUCTION

Cardiovascular diseases (CVDs) are the main cause of death in the world, responsible for 17.9 million deaths each year.[1] In Brazil, CVDs account for 30% of the 72% of deaths due to chronic non-communicable diseases, numbers that may be affected by the Covid-19 pandemic, caused by the Sars-CoV-2 virus.[2,3] Although obesity, diabetes, hypertension, and hyperlipidemia are classified as modifiable risk factors for CVDs, projections for 2030 indicate that CVDs will create a significant global financial cost of US$1,044 billion.[1]

Metabolic syndrome (MetS) has a strong association with CVDs. This syndrome is characterized by the combination of three or more factors that predispose to the development of cardiovascular events, namely abdominal obesity, high blood pressure, fasting glucose, and triglycerides (TGL), in addition to a reduction in the high density lipoprotein (HDL-c).[4]

MetS affects 20 to 25% of the world's adult population and is related to increased overall mortality.[5,6] In Brazil, a cross-sectional study showed a prevalence of MetS of 38.4% in the adult population.[7] It is estimated that male individuals with MetS are three times more likely to develop CVD than those without MetS.[5]

In addition to the established action of vitamin D on the musculoskeletal system, low vitamin D concentration has been associated with MetS. Vitamin D concentration has shown a negative correlation with MetS components, such as hypertriglyceridemia and insulin resistance.[8] This vitamin probably counteracts obesity-induced inflammation by blocking early adipogenesis and increasing glucose uptake.[9] In addition, vitamin D has shown multiple pathophysiological mechanisms that suggest involvement in the development of CVDs, such as negative regulation of the renin-angiotensin system, expression of vascular endothelial growth factor, anti-hypertrophic properties, and stimulation of cell proliferation of vascular smooth muscle.[10] Evidence suggests that 25-hydroxyvitamin D 25(OH)D deficiency is significantly associated with increased cardiovascular risk.[11,12]

Risk estimates can contribute to the population's awareness of CVDs, motivating adherence to lifestyle changes, or indicating the introduction of treatment for high blood pressure and other medications. There are different methods of early prediction of CVD risk. Among the cardiovascular risk assessment methods, there is the Framingham Risk Score (FRS), widely used to estimate cardiovascular risk in the following 10 (ten) years. The FRS considers the following cardiovascular risk factors: age, gender, diabetes, HDL-c, smoking, and systolic blood pressure.[6,13,14] This instrument is one of the cardiovascular risk assessment methods recommended by the Brazilian Society of Cardiology.[15]

Given the above, the aim of this study was to assess the risk of developing CVD according to vitamin D status in individuals with MetS.

METHODS

This is a cross-sectional study, developed with adult individuals (18-59 years old) of both genders, diagnosed with MetS and selected at the Endocrinology Outpatient Clinic of the University Hospital Onofre Lopes – HUOL (UFRN). MetS was diagnosed according to the National Cholesterol Education Program - Adult Treatment Panel III (NCEP-ATP III)[16] (2002), which includes the presence of at least three of the following criteria: waist circumference (WC)> 102 cm in men and > 88 cm in women; TGL≥ 150 mg/dL; HDL-c < 40 mg/dL in men and < 50 mg/dL in women; blood pressure ≥ 130 mmHg and/or ≥ 85 mmHg or use of antihypertensive drugs and fasting blood glucose ≥ 100 mg/dL or use of oral hypoglycemic agents. The study

was approved by the Research Ethics Committee of HUOL, under CAAE nº 13699913.7.0000.5292. All participants signed an informed consent form.

Exclusion criteria were individuals using insulin, glucocorticoids in the last three months, supplemented with calcium and/or vitamin D and derivatives in the last 30 days, and under treatment with antiepileptic drugs or rifampicin, as well as individuals with changes in renal and hepatic function (renal: clearance estimated by the MDRD < 60 mL/min; hepatic: values three times above the reference range for transaminases), decompensated heart failure, and pregnant or lactating.

Individuals who met the pre-established inclusion criteria were invited to participate voluntarily and informed about the research objectives.

Demographic variables and smoking

Data related to age, gender, use of medication and smoking were collected. Smoking was assessed in relation to "use in life", non-smokers were considered those who smoked less than 100 cigarettes during their lifetime; ex-smokers, when they smoked at least 100 cigarettes during their lifetime and have not smoked for at least one year; and smokers, when they smoked more than 100 cigarettes during their lifetime and continue to smoke.[17]

25(OH)D status analysis

Analysis of 25(OH)D in serum was performed by the chemiluminescence method using the DiaSorin® kit, Liaison® chemiluminescent assay (Italy). The established criterion for classifying 25(OH)D status was deficient < 20 ng/mL; insufficient≤ 29 ng/mL and sufficient ≥ 30 ng/mL.[18]

Analysis of the lipid profile and blood glucose

'Venous blood was collected after a 12-hour fast. The analyzes of fasting glucose, HDL-c, low density lipoprotein (LDL-c) and TGL concentrations were performed by colorimetric assay, using the Wiener lab® kit (Wiener LabGroup, Argentina) with automated equipment (CMD800iX1). The references adopted for the lipid profile followed the recommendations of the NCEP-ATPIII:[16] HDL-c < 40 mg/dL for men and < 50 mg/dL for women; TGL ≥ 150 mg/dL; LDL-c ≥ 130 mg/dL; and fasting blood glucose ≥ 100 mg/dL.

Anthropometric assessment and blood pressure

Body mass index (BMI) was calculated according to the ratio of weight by height squared (weight/height²), as classified according to the World Health Organization.[19] WC was measured in duplicate and the average of these values was considered. For WC classification, the criteria recommended by the NCEP-ATPIII were used.[19]The assessment of systolic blood pressure (SBP) and diastolic blood pressure (DBP) was performed according to the procedures established by the 7th Brazilian Guideline on Arterial Hypertension.[15]

Assessment of cardiovascular risk

Participants were classified according to the risk of developing CVD over ten years, through the application of the FRS, which measures the score of risk factors such as age, gender, LDL-c, HDL-c, smoking, diabetes, and arterial blood pressure. The absolute risk score for developing CVD was categorized into low risk (10%), intermediate risk (10-20%) and high risk (>20%).

Statistical analysis

In the analysis of continuous variables, the Kolmogorov-Smirnov test was performed to assess the normality of data distribution, subsequently calculating the mean and standard deviation (SD) or median (interquartile range), when appropriate. Absolute and relative frequencies were calculated for binary and categorical variables. Chi-square test was used to establish association between 25(OH)D status and FRS. For this, the 25(OH)D status was grouped into two categories, that is, "inadequate" (deficient and insufficient) and "adequate" (sufficient). The FRS was also grouped into categories, by combining "intermediate risk" and "high cardiovascular risk", resulting in a new category called "high risk". Finally, two categories were established: "low risk" and "high risk". The α level of significance considered was 5% (or $P < 0.05$, two-tailed) for all analyses. SPSS 20.0 software was used.

RESULTS

Of the 161 individuals, 79.5% were female, with a mean age of 45 (9.3) years. We recorded that 39.1% had sufficient 25(OH)D status and most individuals, 64.6%, had never smoked. Regarding the use of medication, it was observed that 105 individuals used antihypertensive drugs (Table 1).

Table 1. General characteristics of individuals with metabolic syndrome (n=161), Natal, RN, 2020.

Variables	n	%
*Age (years)**	45 (9.3)	-
Sex		
Male	33	20.5
Female	128	79.5
Use of antihypertensive		
Yes	105	65.2
No	56	34.8
Use of hypoglycemic agents		
Yes	84	52.2
No	77	47.8
*Use of lipid-lowering agents***		
Yes	43	26.7
No	114	70.8
Smoking		
Smoker	10	6.2
Non-smoker	104	64.6
Ex-smoker	47	29.2
25(OH)D status		
Deficient	30	18.6
Insufficient	68	42.2
Sufficient	63	39.1

*Mean (standard deviation). ** n= 157.

Table 2 shows the high means for BMI and WC, corresponding to 32.7 (29-40) kg/m² and 102.5 (96-114) cm respectively. Regarding the concentration of 25(OH)D, a mean of 29.7 (21-34) ng/mL was observed, indicating insufficient status of 25(OH)D in the population (less than 30 ng/mL).

Table 2. Clinical and biochemical characteristics of individuals with metabolic syndrome (n=161), Natal, RN, 2020

Variables	Mean (Q25-Q75)
BMI (kg/m²)	32.7 (29-40)
WC (cm)	102.5 (96-114)
LDL-c (mg/dL)*/**	136.0(49.9)
HDL-c (mg/dL)	39.0 (33-47)
Triglycerides(mg/dL)***	165.5 (119-236)
SBP (mm/Hg)	130.0 (120-140)
DBP (mm/Hg)	90.0 (80-90)
Fasting blood glucose(mg/dL)	107.0 (95-128)
25(OH)D (ng/mL)	29.7 (21-34)
FRS Classification****	
Low risk	92 (57.1)
Intermediate risk	41 (25.5)
High risk	28 (17.4)

*Mean (standard deviation). **Data shown with n= 152. ***Data shown with n= 158. ****Data shown as n(%). BMI, body mass index; WC, waist circumference; LDL-c, low-density lipoprotein; HDL-c, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; FRS, Framingham risk score.

The application of the FRS resulted in 57.1% of individuals classified as low risk; 25.5% as intermediate risk; and 17.4% were at high risk of developing CVDs. When grouping individuals with deficient and insufficient status of 25(OH)D, 60.8% of these presented inadequate values. After grouping individuals with intermediate and high risk (FRS), 42.9% were at high risk of developing CVDs. There was no significant association between vitamin D status and higher cardiovascular risk assessed by FRS (p= 0.514), as shown in Table 3.

Table 3. Association between cardiovascular risk according to vitamin D status of individuals with metabolic syndrome. Natal, RN, 2020.

Cardiovascular riskassessed byFRS*	Vitamin D status**		PR	CI 95%	p-value***
	Inadequate n (%)	Adequate n (%)			
Lowrisk	54 (55.1)	38 (60.3)	0.91	0.70-1.20	0.514
Highrisk	44 (44.9)	25 (39.7)	1.13	0.78-1.65	

*FRS, Framingham risk score: Low cardiovascular risk <10%; High risk ≥ 10%23; **Adequate vitamin D status ≥ 30.0ng/mL and inadequate ≤ 30.0ng/mL18; ***Pearson Chi-Square Test; PR, prevalence ratio; CI, confidence interval.

DISCUSSION

In the present study, no association was observed between the risk of developing CVD and vitamin D status in individuals with MetS. Differing results were reported by Heidari[21] and Zarooni et al.,[22] who observed that 25(OH)D deficiency was associated with increased cardiovascular risk assessed by FRS. Although some observational and experimental studies have reported an association between low concentrations of vitamin D and increased cardiovascular risk, randomized clinical trials have failed to demonstrate a causal relationship, and controversy remains about the exact effect of vitamin D on CVDs.[10,23]

In the study, most participants were at low risk of developing CVD over the next ten years, according to the FRS. The lack of coverage of several MetS characteristics by the FRS, such as obesity and hypertriglyceridemia, may have influenced the prediction of cardiovascular risk in this population, considering that these components are predictive factors of adverse cardiovascular events.[6] It should be noted that the estimate of "low risk" does not mean "no risk", especially in the prediction of cardiovascular risk for more than 10 (ten) years. Considering that a patient lives for the next ten years, obviously their risk estimate will increase over time, due to the high dependence on age as a risk assessment tool.

It is estimated that MetS occurs in 30 to 40% of patients with arterial hypertension, and high blood pressure is one of the main cardiovascular risk factors. Although the participants in this study were treated at a multidisciplinary outpatient clinic and most used antihypertensive drugs, the individuals still had blood pressure measurements above the recommended level. This suggests the absence of a combination of adopting healthier lifestyles and drug treatment, a strategy that can contribute to the effectiveness of drug therapy.

This study also demonstrated that most individuals with MetS had inadequate vitamin D. This predominance can be explained, in part, by anthropometric indices suggestive of obesity, such as BMI and WC. When adipose tissue takes up lipids from chylomicrons, a fraction of vitamin D, which is a fat-soluble vitamin, is taken up by this tissue.[25]It has been speculated that vitamin D is accumulated in adipose tissue, indicating that vitamin D storage in body fat can decrease its bioavailability. Furthermore, vitamin D metabolizing enzymes, such as 25-hydroxylase (CYP2R1, CYP27A1, CYP2J2), 1α-hydroxylase (CYP27B1), and catabolic 24-hydroxylase (CYP24A1), are expressed in adipose tissues. Based on this condition, adipose tissues play an active role in the metabolism of vitamin D, contributing to the low concentration of vitamin D

in individuals with obesity.[26] In addition, individuals with MetS may not be sufficiently exposed to sunlight due to the decrease in mobility caused by obesity and aging , which, in turn, may influence the concentration of 25(OH)D in serum.[27]

It was noted that 79.5% of the study participants were women with an average age of 45 years. Thus, a high prevalence of low concentrations of 25(OH)D has been related to the postmenopausal state, considering that reduced estrogen concentrations influence of vitamin D deficiency .[28]

In individuals with MetS, vitamin D inadequacy may be negatively correlated with some components of MetS, such as glycemia, blood pressure, and TGL.[9]Furthermore, vitamin D deficiency may be related to an imbalance in vascular homeostasis, which compromises arterial function, increasing the progression of cardiovascular events in different populations.[28]

This study has some limitations. The cardiovascular risk assessment instrument, even though it is a method that is easily applied in daily life and useful for predicting the risk of developing CVD, is highly dependent on age. This fact can cause some underestimation of cardiovascular disorders at young ages including obesity and hypertriglyceridemia.[6] The cross-sectional study design cannot be used to deduce causal relationship. In addition, there was a predominance of females in the studied population. On the other hand, the use of internationally accepted criteria to diagnose MetS and the standardization of the anthropometric assessments are considered important strengths of the study. It is noteworthy that sun exposure and food consumption of the individuals in the present study were evaluated in previous studies.[29,30]

Therefore, it is necessary to carry out further studies with a longitudinal temporality and with a larger sample size, to better understand the impact of vitamin D in the prevention and/or treatment of CVD in individuals with MetS and to broaden the discussion about the effects of vitamin D in the body .

CONCLUSION

Inadequate 25(OH)D status was not significantly associated with cardiovascular risk among individuals with MetS. Most subjects had deficiency or insufficiency of 25(OH)D in serum. These results reinforce the importance of clinical monitoring to prevent the impacts of hypovitaminosis D on patients with MetS.

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Contributors

Silva LC, Aquino SLS and Pedrosa LFC participated in all stages, from study design to review of the final version of the article; Cunha ATO worked on data collection and analysis of results; Lima JG participated in the study design, data interpretation, and final revision of the article.

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