

RELATIONSHIP BETWEEN CAROTID ARTERY THICKNESS, VITAMIN D, GLYCEMIC PROFILE AND ANTHROPOMETRY

Ricardo José Tofano

Cardiologist at the Associação Beneficente Hospital Universitário (ABHU); Candidate for a Master's degree in the Postgraduate Program in Structural and Functional Interactions in Rehabilitation – Unimar, Marília SP Brazil.

Lidiane Aparecida Vila Pires

Student of the Course of Medicine at Universidade de Marília (UNIMAR) Marília SP Brazil.

Letícia Maria Pescinni Salzedas

Student of the Course of Medicine at Universidade de Marília (UNIMAR) Marília SP Brazil.

Karina Quesada

Master's Degree in Nutrition by the Faculdade de Medicina de Botucatu (UNESP); professor in the undergraduate course of Medicine and Nutrition, UNIMAR, Marília SP Brazil.

Claudia Rucco Penteadó Detregiachi

Doctor in Nutrition by the Faculdade de Medicina de Botucatu (UNESP), Professor in the undergraduate course in Medicine and Nutrition, UNIMAR; Permanent member of the Postgraduate Program in Structural and Functional Interactions in Rehabilitation – Unimar, Marília SP Brazil.

Marcelo Dib Bechara

Doctor in Genetics by the Faculdade de Medicina de Botucatu (UNESP), Professor in the undergraduate course in Medicine, UNIMAR, Marília SP Brazil.

Sandra Maria Barbalho

Doctor in Sciences by the Universidade Federal de São Carlos (UFSCar), Professor in the undergraduate course in Medicine and Nutrition, UNIMAR; Permanent member of the Postgraduate Program in Structural and Functional Interactions in Rehabilitation – Unimar, Marília SP Brazil.

Corresponding author:

Dra. Sandra Maria Barbalho
sbarbalho@gmail.com

ABSTRACT: The aim of this study was to evaluate the association of carotid intima thickness with vitamin D, glycemia and anthropometry. Personal, anthropometric and biochemical data, and carotid ultrasound report (to check thickening in millimeters and for the presence of atherosclerotic plaques) were collected. The variables studied were treated with Pearson's correlation coefficient, ANOVA and Kruskal-Wallis. The mean BMI of the 51 patients was $29.47 \pm 6.39 \text{ kg/m}^2$. The carotid thickness was $\geq 1 \text{ mm}$ in 54.90%. Regarding vitamin D, 41.18% had hypovitaminosis. The carotid thickness was directly proportionally correlated with anthropometric data, fasting blood glucose and HbA1c, and inversely correlated with vitamin D values, although without significant difference. The studied variables were not significantly associated with carotid intima thickness in this sample.

KEY WORDS: Anthropometry; Carotid; Glycemia; Vitamin D.

RELAÇÃO ENTRE ESPESSURA DA ARTÉRIA CARÓTIDA, VITAMINA D, PERFIL GLICÊMICO E ANTROPOMETRIA

RESUMO: O objetivo foi avaliar se a espessura íntima carotídea está associada à vitamina D, perfil glicêmico e antropométrico. Foram coletados dados pessoais, antropométricos, bioquímicos e laudo de ultrassonografia carotídea, o qual foi utilizado a fim de avaliar o espessamento em milímetros e constatar ou não placas ateroscleróticas. As variáveis estudadas foram tratadas com o coeficiente de correlação de Pearson, ANOVA e Kruskal-Wallis. A média do IMC dos 51 pacientes foi de $29,47 \pm 6,39 \text{ kg/m}^2$. A espessura carotídea foi $\geq 1 \text{ mm}$ em 54,90%. Quanto à vitamina D, 41,18% apresentaram hipovitaminose. A correlação da espessura carotídea com dados antropométricos, glicemia de jejum e HbA1c foi diretamente proporcional e inversamente com os valores de vitamina D, embora sem diferença significativa. As variáveis estudadas não puderam ser associadas com diferença significativa à espessura da camada média intimal da carótida nesta amostra.

PALAVRAS-CHAVE: Antropometria; Carótida; Glicemia; Vitamina D.

INTRODUÇÃO

The intima-media thickness of the carotid wall is a non-invasive marker of subclinical atherosclerosis. This marker has been widely used as a screening method for atherosclerotic lesions and non-asymptomatic plaques. The increased carotid intima-media thickness was associated with risk factors for cardiovascular diseases. It has also been correlated with the extent of coronary artery disease in adults and can predict future cardiovascular events¹.

A growing body of evidence points to the correlation between vitamin D levels and cardiovascular disease. A close link between vitamin D deficiency and carotid atherosclerosis was found in a recent systematic review and meta-analysis, suggesting that patients with hypovitaminosis D may have extra requirements for preventive and therapeutic measures against early atherosclerosis, thus reducing the risk of long-term cardiovascular disease². Additionally, Brazilian population studies demonstrate that the prevalence of hypovitaminosis D in our country is high^{3,4}.

It is also known that patients with coexisting coronary disease and type 2 diabetes mellitus (DM2) are at high risk for cardiovascular events, and that dysregulation of glucose metabolism control is associated with carotid atherosclerosis in patients with coronary disease⁵.

According to a study carried out in low- and middle-income countries, the main factors consistently associated with greater carotid thickness are: age, male gender, systolic blood pressure (SBP), BMI and LDL-c⁶.

However, the association between the carotid thickness with these variables is still contradictory in the literature, therefore, the objective of the present study was to check for the association of carotid intima thickness with vitamin D levels, glycemia and anthropometry in adult and elderly patients.

METODOLOGIA

The study started only after authorization from the institution and the Research Ethics Committee of the University of Marília, State of São Paulo, under Opinion 1.957.920 on 09/03/2017 in accordance with the Ethical

and Legal requirements for research with human beings, as established by the National Health Council.

This was a primary, analytical, observational interference design with a cross-sectional period, single center study.

The study was developed from data collection in medical records of patients seen at a private cardiology clinic in the city of Marília, State of São Paulo. The authorization of the physician responsible for the care of these patients was obtained for the analysis of medical records. In addition to personal identification data (name, sex and age), information was collected on previous diagnosis of diseases or clinical conditions, presence of smoking and alcohol consumption.

Anthropometric data (weight, height, waist circumference and neck circumference), blood pressure, glycemic control tests (fasting glycemia, glycated hemoglobin and insulin), serum vitamin D levels, and the carotid ultrasound report were also collected from patients seen in the period from July 2018 to May 2019. The study included adult and elderly patients who had the data mentioned above available in the medical records, with a maximum interval of three months between examinations (carotid US, serum vitamin D, glycemic data and anthropometric data collection). The anthropometric measurements in the medical records were taken and recorded by trained professionals according to the recommended techniques^{7,8}. With the weight and height, we calculated the Body Mass Index (BMI). The measurement of waist circumference (WC) and neck circumference (NC) was also considered.

Carotid ultrasound reports were used to assess the thickening in millimeters and to check for atherosclerotic plaques, which in turn allow to classify the severity of cardiovascular impairment to later make the association with anthropometric variables, serum vitamin D levels, and glycemic control tests.

In the latest guidelines of the Brazilian Society of Cardiology⁹, the increase in carotid intima-media thickness above 1.0 mm is considered one of the aggravating factors that reclassify individuals in the intermediate to high risk group. Thus, for the classification of the carotid thickness of the sample, we used a reference value of 1.0 mm.

Vitamin D was classified according to the Brazilian Society of Endocrinology and Metabology³ whose reference is vitamin D levels above 20 ng/mL for healthy population (up to 60 years) and for elderly patients, the recommended values are between 30 and 60 ng/mL, and above 100 ng/mL, it is already considered a risk of toxicity and hypercalcemia.

The statistical treatment of quantitative data was carried out using the BioEstat 5.0 software. Data were presented in tables of frequency or mean \pm standard deviation and median. For the association of the studied variables, we applied appropriate tests, among them, Pearson's correlation coefficient, ANOVA (1 criterion) and Kruskal-Wallis, depending on the variance of the data to be analyzed. The probability of significance considered was 5% ($p < 0.05$) for the operations performed.

RESULTS

Among the 51 medical records of the patients analyzed, 50.98% were male and 49.02% were female, whose mean age was 60.59 ± 9.94 years (minimum 29 years and maximum 84 years).

Of this total, 54.90% patients presented atheromatous plaques on carotid ultrasound, with 17 (60.71%) male patients and 11 (39.29%) female patients, with a significant difference between the sexes ($p = 0.002$).

Comparing these patients who presented atheromatous plaques in the carotids with patients without plaques, the mean age was higher in patients with atherosclerosis (62.32 ± 7.87 years in patients with plaques; 58.48 ± 11.89 years in patients without plaques). There was also a higher prevalence of patients previously diagnosed with Systemic Arterial Hypertension (SAH) and a higher percentage of smokers in those who had atherosclerosis (Table 1).

Table 1. Comparison between the two groups presented with the risk factors associated with cardiovascular diseases

	Patients with atherosclerosis		Patients without atherosclerosis	
	n altered (28)	%	n altered (23)	%
Diabetes Mellitus tipo 2	6	21.43%	8	34.78%
Systemic Arterial Hypertension	24	85.71%	16	69.57%
Alcoholic	8	28.57%	8	34.78%
Smoker	11	39.29%	4	17.39%

Among patients who had atheroma plaques, 60.71% showed a relative deficit of vitamin D, while 47.83% patients who did not have atherosclerosis on carotid ultrasound also had a deficit of this vitamin, but with no significant difference (Table 2).

Table 2. Comparison of anthropometric, biochemical and systolic blood pressure variables between patients with atherosclerosis and without atherosclerosis

	Patients with atherosclerosis					Patients without atherosclerosis					p-value
	Mean	SD	Median	n altered	%	Mean	SD	Median	n altered	%	
BMI	29.65	7.60	28.85	20	71.43%	29.25	4.66	29	20	86.96%	0,5411*
WC	103.05	16.45	101	17	60.71%	100.26	15.45	102.5	15	53.57%	0,5453*
NC	39.82	3.86	40	26	92.86%	38.23	4.91	38	16	57.14%	0,2013*
Glycemia	102.25	17.51	97.5	11	39.29%	112.78	41.29	105	15	65.22%	0,3582**
HbA1c	6.19	1.94	5.6	11	39.29%	5.67	0.75	5.3	5	21.74%	0,2256**
Insulin	18.93	24.60	11.29	17	60.71%	11.47	5.62	11.1	13	56.52%	0,6771**
VIT D	27.32	9.53	27	14	50.00%	31.56	13.49	32	7	30.43%	0,1920*
SBP	129,82	16,13	127,5	14	50.00%	135,0	19,71	135,0	14	60.87%	0,3078*

*ANOVA (1 critério). **Kruskal-Wallis. SD: Standard deviation.

BMI: Body Mass Index. WC: Waist Circumference. NC: Neck Circumference. HbA1c: Glycated. VIT D: Vitamin D. SBP: Systolic Blood Pressure.

When correlating the thickness of the right and left carotid arteries with age, significant results ($p < 0.05$) were directly proportional, indicating that, with increasing age, there is an increase in the thickness of both carotids. And when associating the thickness of the right and left carotid arteries with anthropometric data (body mass index, waist circumference and neck circumference), a directly proportional relationship was found, but with no significant difference (Figure 1).

In the correlation of the thickness of the right and left carotid arteries to the glycemic profile (fasting glycemia, glycated hemoglobin and insulin), the results obtained were inversely proportional, but with no significant difference. The HbA1c and fasting blood glucose levels were directly proportional to the carotid thickness, although also with no significant difference (Figure 2).

The correlation of the carotids with serum levels of vitamin D was also estimated, which showed an inversely proportional value, with no significant difference ($r = -0.1200$ and $p = 0.4015$); and, when correlating with systolic blood pressure, values were directly proportional ($r = 0.2439$ and $p = 0.0845$).

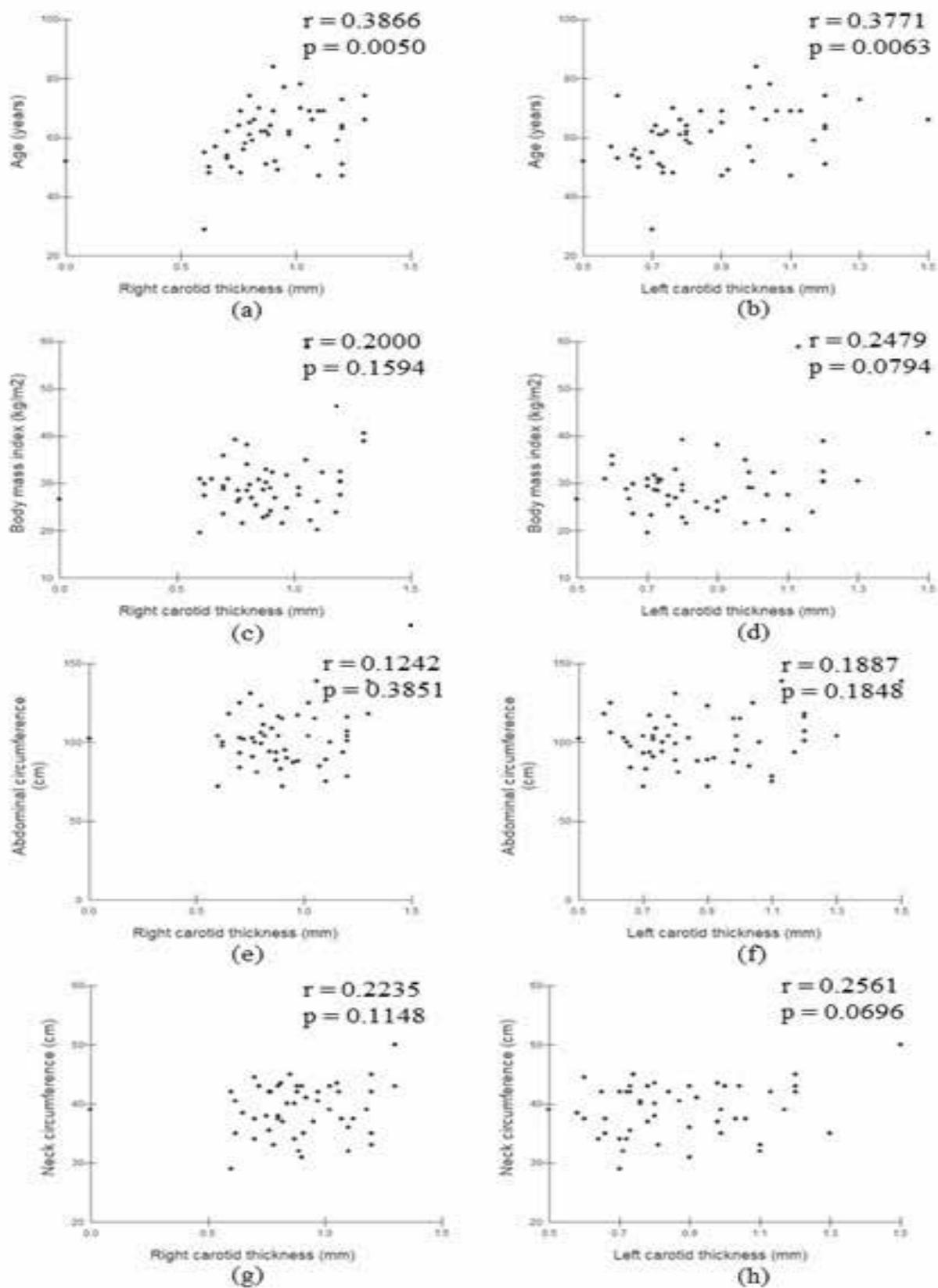


Figure 1. Correlation between age and anthropometric parameters with the thickness of the right and left carotid arteries. (a) Age and thickness of the right carotid artery. (b) Age and thickness of the left carotid artery. (c) Body mass index and thickness of the right carotid. (d) Body mass index and thickness of the left carotid. (e) Abdominal circumference and thickness of the right carotid. (f) Abdominal circumference and thickness of the left carotid. (g) Neck circumference and thickness of the right carotid. (h) Neck circumference and thickness of the left carotid artery.

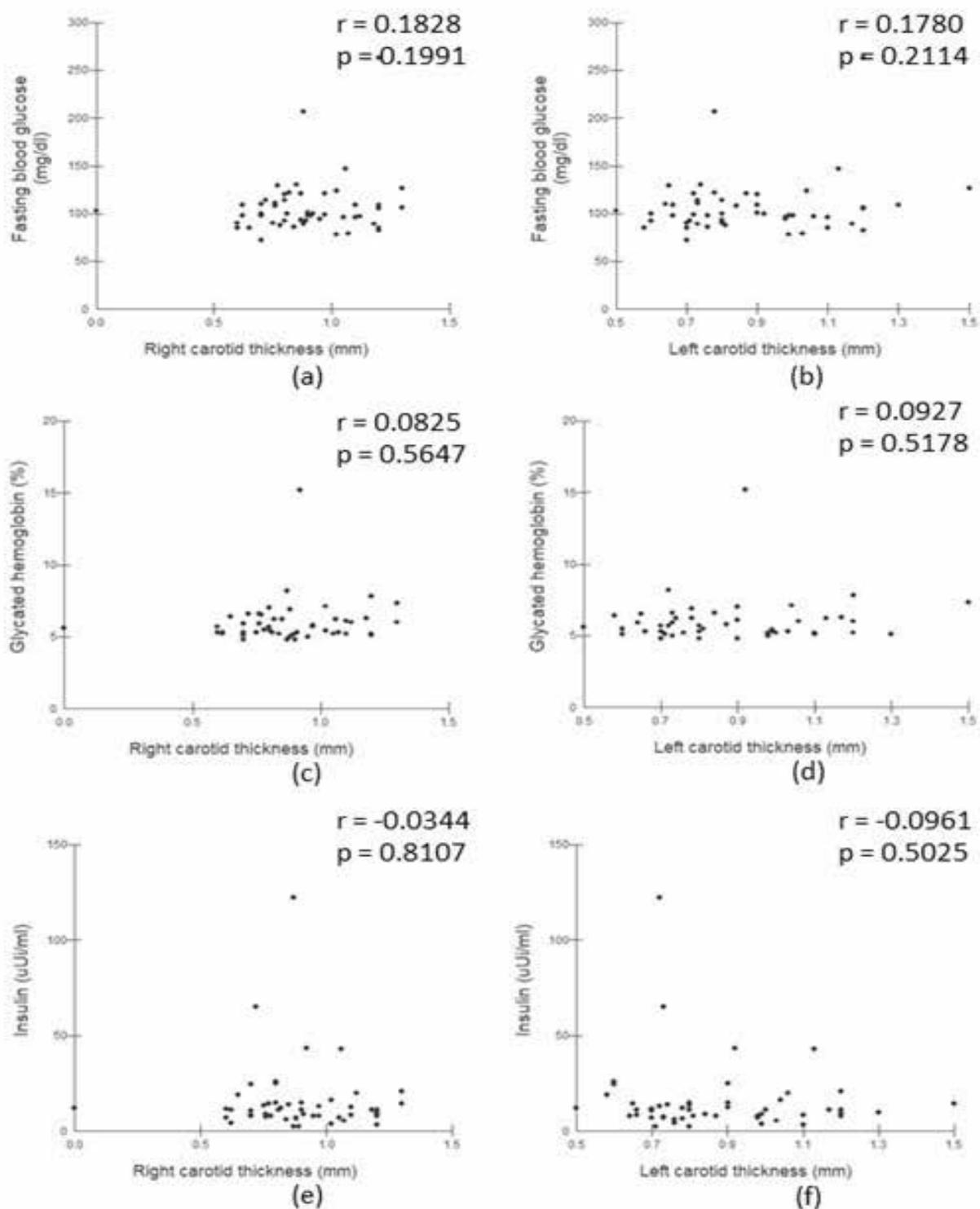


Figure 2. Correlation between the glycemic profile and the thickness of the right and left carotid arteries. (a) Fasting blood glucose and direct carotid thickness. (b) Fasting blood glucose and left carotid thickness. (c) Glycated hemoglobin and thickness of the right carotid. (d) Glycated hemoglobin and thickness of the left carotid. (e) Insulin and thickness of the right carotid. (f) Insulin and thickness of the left carotid.

DISCUSSION

The results of this study showed that there was a greater number of patients who had atherosclerosis plaques with relative vitamin D deficiency compared to patients who did not have this comorbidity. Furthermore, when correlating vitamin D with carotid thickness, inversely proportional values were obtained, but with no significant difference ($p > 0.05$). Brazilian population studies demonstrate that the prevalence of hypovitaminosis D in our country is high.¹⁰ However, the association of the thickness of the right/left carotid with this variable is still contradictory in the literature.

Unlike our results, Chen et al.² revealed, in a meta-analysis, a close link between hypovitaminosis D and carotid atherosclerosis, regardless of conventional risk factors. From a clinical perspective, their results suggested that low serum vitamin D levels should be recognized as a possible risk factor for atherosclerotic cardiovascular diseases. Interestingly, a cohort study of HIV-positive patients in Canada also found a lower baseline level of vitamin D associated with greater vascular disease progression, when the thickness of the carotid intima-media layer was assessed.¹¹ And, despite inconsistent results, the meta-analysis of a prospective study of mortality from cardiovascular disease suggests an inversely linear association between vitamin D and risk of developing cardiovascular disease with a threshold of 25(OH) below 60 nmol/L.¹²

Askarian et al.¹³ found a negative correlation between vitamin D levels and average thickness of the right/left carotid in patients undergoing hemodialysis ($r = -0.096$ / $p = 0.508$, $r = -0.008$ / $p = 0.953$, respectively), however, also found no significant difference. Likewise, Lee et al.¹⁴ found no association between hypovitaminosis D and atherosclerosis indices in Korean patients.

In another study, with a significant difference, it was demonstrated that the absolute risk of the presence of carotid plaques was 37.0% in 1,889 patients with vitamin D deficiency and 23.7% in 2,883 control patients.¹⁵

Wang et al.¹⁶, in addition to suggesting that the decrease in serum vitamin D levels showed a tendency to increase the carotid intima-media thickness and the

number of carotid plaques, also showed that patients in the group that had carotid plaque were older, had higher SBP and higher levels of HbA1c. Similarly, in our study, the group with carotid atherosclerosis was older (mean age 62.32 ± 7.87 years) and had higher levels of HbA1c ($p > 0.05$). However, it proved to be the opposite, when analyzing systolic blood pressure ($p > 0.05$).

A study carried out by Shui et al.¹⁷ showed that the carotid intima-media thickness is directly proportional to the fasting blood glucose values (with $p < 0.001$). Our data also show that fasting blood glucose values were directly proportional to carotid thickness, although with no significant difference, as illustrated in Figure 2. Patients with carotid atherosclerosis have a higher average values of fasting blood glucose when compared to patients without atherosclerosis, although also with no significant difference (table 2).

Dash et al.¹⁸, in their study comparing patients with and without a family history of diabetes mellitus, reported an increase in insulin resistance and an increase in carotid thickness in patients with a family history of diabetes mellitus, although with no significant difference. When correlating serum levels of glycemia, glycated hemoglobin and BMI with carotid thickness, they obtained values directly proportional and with significant difference. Our study, when correlating such data, although they were also directly proportional, evidenced no significant difference for any of the variables mentioned.

In the present study, male patients are more likely to have atheromatous plaques in the carotid arteries than women, with a significant difference ($p = 0.002$). Another study, carried out in Africa, found similar results, also with a significant difference.⁶

As for the correlation of anthropometric data with carotid thickness, our study showed that BMI, waist and neck circumferences were directly proportional to the thickness of the right and left carotid arteries, although with no significant difference for any of the variables, as shown in Figure 1. Eickemberg et al.¹⁹ showed that waist circumference was the indicator most strongly associated with carotid thickness. Jin et al.²⁰ also verified an association between obesity rates and carotid intima-media thickness in office workers in Korea. Winckler et

al.21 found a positive association of intima-media carotid thickness, but without significant difference, with sex, age, BMI, smoking, systolic blood pressure, total cholesterol, and HbA1C.

CONCLUSION

The results of this study suggest a positive association of carotid thickness and anthropometric data (BMI, waist and neck circumference), fasting blood glucose, HbA1c and blood pressure. For the vitamin D and insulin, there was a negative association. However, the association was not significant for any of the variables. There was a significant positive association only between carotid thickness with the age of the participants and with the male gender.

A limitation of this study was the small number of patients analyzed. In a larger population, perhaps such correlations could be different. The high prevalence of cardiovascular disease, which is associated with higher mortality in individuals with changes in anthropometric variables, blood glucose and serum vitamin D concentrations assessed in our study may be additional requirements for preventive and therapeutic measures against early carotid atherosclerosis.

REFERENCES

1. Wang P, Xu YY, Lv TT, Guan SY, Li XM, Li XP, et al. Subclinical Atherosclerosis in Patients With Type 1 Diabetes Mellitus: A Systematic Review and Meta-Analysis. *Angiology*. 2019 Feb;70(2):141-159.
2. Chen F, Liu T, Xu L, Zhang L, Zhou X. Association of Serum Vitamin D Level and Carotid Atherosclerosis A Systematic Review and Meta-analysis. *J Ultrasound Med*. 2018 Jun;37(6):1293-1303.
3. Ferreira CES, Maeda SS, Batista MC, Lazaretti-Castro M, Vasconcellos LS, Madeira M, et al. Posicionamento Oficial da Sociedade Brasileira de Patologia Clínica/Medicina Laboratorial (SBPC/ML) e da Sociedade Brasileira de Endocrinologia e Metabologia (SBEM) – Intervalos de Referência da Vitamina D - 25(OH) D. 2018.
4. Khosravi ZS, M Kafeshani, Tavasoli P, Zadeh AH, Entezari MH. Effect of Vitamin D supplementation on weight loss, glycemic indices, and lipid profile in obese and overweight women: A clinical trial study. *International Journal of Preventive Medicine*. 2018; 9(1): 63.
5. Brauna C, Vieira RFFA, Kuhl AM, Melhen ARF, Benemann GD, Schiessel DL et al. Análise da efetividade de estratégia nutricional em mulheres com síndrome metabólica. *Saúde e Pesqui*. 2019 maio-ago; 12(2): 241-251
6. Nonterah EA, Boua PR, Klipstein-Grobusch K, Asiki G, Micklesfield LK, Agongo G, et al. Classical Cardiovascular Risk Factors and HIV are Associated With Carotid Intima-Media Thickness in Adults From Sub-Saharan Africa: Findings From H3Africa AWI-Gen Study. *J Am Heart Assoc*. 2019 Jul 16;8(14):e011506. doi: 10.1161/JAHA.118.011506. Epub 2019 Jul 13.
7. Lohman TG, Roche AF, Martorell R. Anthropometric standardization reference manual. Abridged Edition. 1988.
8. Gibson R.S. Principles of nutritional assessment. 2^o Edition, Oxford University Press, 2005.
9. Freire CMV, Alcantara ML, Santos SN, Amaral SI, Veloso O, Porto CLL, et al. Recomendação para a Quantificação pelo Ultrassom da Doença Aterosclerótica das Artérias Carótidas e Vertebrais: Grupo de Trabalho do Departamento de Imagem Cardiovascular da Sociedade Brasileira de Cardiologia – DIC – SBC. *Arq Bras Cardiol: Imagem cardiovasc*. 2015 Abril; 28(nº especial):e1- e64.
10. Ferreira D, de Bragança AC, Volpini RA, Shimizu MHM, Gois PHF, Girardi ACC, et al. Vitamin D deficiency is a potential risk factor for lipid Amphotericin B nephrotoxicity. *PLoS Negl Trop Dis*. 2019 Jul 11;13(7).
11. Huff H, Merchant AT, Lonn E, Pullenayegum E, Smaill F, Smieja M. Vitamin D and progression of carotid intima-media thickness in HIV-positive Ca-

- nadians. *HIV Med.* 2018 Feb;19(2):143-151.
12. Wang L, Song Y, Manson JE, Pilz S, März W, Michaëlsson K, et al. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. *Circ Cardiovasc Qual Outcomes.* 2012 Nov;5(6):819-29.
 13. Askarian F, Ghorbanihaghjo A, Argani H, Sanajou D, Nasehi N, Askarian R, et al. Soluble Tumor Necrosis Factor Like Weak Inducer of Apoptosis and Vitamin D in Hemodialysis Patients: Relation to Carotid Intima-Media Thickness. *Indian J Clin Biochem.* 2018 Jul;33(3):297-303.
 14. Lee YH, Kweon SS, Choi JS, Nam HS, Park KS, Choi SW, et al. Association of serum vitamin D and parathyroid hormone with subclinical atherosclerotic phenotypes: The Dong-gu Study. *PLoS One.* 2017 Oct 31;12(10):e0186421.
 15. Lupoli R, Vaccaro A, Ambrosino P, Poggio P, Amato M, Di Minno MN. Impact of Vitamin D deficiency on subclinical carotid atherosclerosis a pooled analysis of cohort studies. *J Clin Endocrinol Metab.* 2017 May 9.
 16. Wang Y, Zhang H. Serum 25-Hydroxyvitamin D₃ Levels Are Associated with Carotid Intima-Media Thickness and Carotid Atherosclerotic Plaque in Type 2 Diabetic Patients. *J Diabetes Res.* 2017;2017:3510275.
 17. Shui W, Zhang YQ, Zhang YF, Zhang Q, Zhao M, Xi B. Association of abnormal metabolic indices and its clustering with carotid intima-media thickness in childhood. *Zhonghua Yu Fang Yi Xue Za Zhi.* 2019 Jul 6;53(7):692-695.
 18. Dash DK, Choudhury AK, Singh M, Mangaraj S, Mohanty BK, Baliarsinha AK. Effect of parental history of diabetes on markers of inflammation, insulin resistance and atherosclerosis in first degree relatives of patients with type 2 diabetes mellitus. *Diabetes Metab Syndr.* 2018 May;12(3):285-289.
 19. Eickemberg M, Amorim LDAF, Almeida MDCC, Aquino EML, Fonseca MJMD, Santos IS, et al. Indicators of Abdominal Adiposity and Carotid Intima-Media Thickness: Results from the Longitudinal Study of Adult Health (ELSA-Brazil). *Arq Bras Cardi-ol.* 2019 Mar;112(3):220-227.
 20. Jin Y, Kim D, Cho J, Lee I, Choi K, Kang H. Association between Obesity and Carotid Intima-Media Thickness in Korean Office Workers: The Mediating Effect of Physical Activity. *Biomed Res Int.* 2018 Aug 1; 2018:4285038.
 21. Winckler K, Tarnow L, Lundby-Christensen L, Almdal TP, Wiinberg N, Eiken P, et al. Vitamin D, carotid intima-media thickness and bone structure in patients with type 2 diabetes. *Endocr Connect.* 2015; 4:128–135.