BRIEF ARTICLE

Basal Glucose and HbA1c Associated with Carotid Plaques in non-Diabetics: an Approach with CHAID Trees

Glucemia basal y HbA1c asociados a placas carotídeas en no diabéticos: un enfoque con árboles CHAID

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ABSTRACT

Background: Carotid plaques are significant markers of risk for stroke.
Objective: The aim of this research was to analyze the association between baseline glycemia and glycated hemoglobin (HbA1c) with the presence of carotid plaques in non-diabetic adults.
Methods: We conducted a cross-sectional analytical study using a secondary database. The variables considered included carotid plaque score, baseline glycemia and HbA1c. The CHAID decision tree was utilized in this analysis.
Results: The CHAID tree classified baseline blood glucose levels > 104 mg/dL along with HbA1c values > 6%. as the most decisive variables associated with the presence of carotid plaques at risk for stroke. The odds of presenting with a high-risk carotid plaque score was 3.69 times higher for these patients when compared to those with lower glucose and HbA1c levels (OR 3.69; 95% CI, 2.59-5.28). Patients with the aforementioned blood glucose levels and HbA1c had greater probability of a true positive result for high-risk carotid plaque (LR+ 3.29; 95% CI, 2.38-4.54). In these patients, the median carotid plaque score was 1.60 compared to 0.25 in those with lower values (p=0.001). The median number of plaques was also greater (1.20 vs. 0.30; p < 0.001).
Conclusions: Baseline blood glucose levels >104 mg/dL and HbA1c >6% were associated with the presence of high-risk carotid plaques in non-diabetic patients.

Keywords: Plaque, Atherosclerotic - Ultrasonography, Carotid Arteries - Glycated Hemoglobin - Blood Glucose - Primary Health Care

RESUMEN

Introducción: La presencia de placas carotídeas es un importante marcador de riesgo de accidente cerebrovascular (ACV).
Objetivo: Analizar la asociación entre valores de glucemia basal y hemoglobina glicosilada (HbA1c) con la presencia de placas carotídeas en adultos no diabéticos.
Material y métodos: Estudio analítico de corte transversal con la utilización de una base de datos secundaria. Las variables consideradas incluyeron: puntaje de placas carotídeas, glucemia basal y HbA1c. Se empleó el árbol de decisiones CHAID.
Resultados: El árbol CHAID identificó que una glucosa basal de 104 mg/dL con HbA1c >6 % es la característica principal asociada a presencia de placas carotídeas de riesgo para ACV. Los pacientes con estas características tuvieron 3,69 veces más a menudo placas carotídeas de riesgo que aquellos con valores menores de glucosa y HbA1c (OR 3,69; IC95% 2,59-5,28). Los valores citados de glucemia basal y HbA1c tuvieron probabilidad significativamente mayor de corresponder a un verdadero positivo que a un falso positivo para señalar la presencia de placas de riesgo (LR+ 3,29; IC95% 2,38-4,54). La mediana de puntaje de placas carotídeas fue de 1,60 en estos pacientes, comparado con 0,25 en aquellos con valores menores (p=0,001). También tuvieron una mediana mayor de número de placas (1,20 vs. 0,30; p<0,001).
Conclusiones: Valores de glucemia basal >104 mg/dL con HbA1c >6 % se asociaron a mayor presencia de placas carotídeas de riesgo en pacientes no diabéticos.

Palabras clave: Placa Aterosclerótica - Ultrasonografía carotídea - Hemoglobina Glicosilada - Glucemia - Riesgo cardiovascula

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INTRODUCTION

Atheromatous plaques are accumulations of macrophages, T cells, dendritic cells, calcium, lipids, and fibrous connective tissue in the inner layer of arteries. (1) These plaques narrow the arterial lumen and cause micro-ruptures, increasing the risk of thromboembolic and ischemic events such as myocardial infarction and stroke. (2) Atherosclerosis, a chronic inflammatory disease, is influenced by factors such as dyslipidemia, dysglycemia, smoking, diets high in fat and carbohydrates, sedentary lifestyle, age and genetic predisposition. (3)

Carotid artery stenosis due to atherosclerosis causes about 10-20% of all ischemic strokes by two main mechanisms: hemodynamic impairment in case of significant stenosis, and thromboembolism from an atherosclerotic plaque regardless of the degree of stenosis. (4) Stroke is the second leading cause of death and the third leading cause of morbidity and mortality worldwide, (5) especially ischemic stroke, which accounts for 85% of cases. (6) Hyperglycemia, mainly in type 1 and 2 diabetes mellitus, promotes atherosclerosis through mechanisms such as the formation of advanced glycation end-products, oxidative stress and alteration of endothelial growth factor. (7)

Given that the relationship between glycemia and atherosclerosis is not limited to patients with diabetes or prediabetes, it is crucial to understand the glycemic profile associated with carotid artery atherosclerosis in subjects without dysglycemia. The use of the chi-squared automatic interaction detection (CHAID) decision tree analysis can help to identify this profile. The aim of this research was to analyze the association between baseline blood glucose levels and HbA1c with the presence of carotid plaques in non-diabetic adults.

METHODS

Study design and population

We conducted an analytical and cross-sectional study, based on an international database registered in the Dryad repository (https://datadryad.org). The research was triggered after reading the article "Mathematical modeling for the prediction of cerebral white matter lesions based on clinical examination data", (8) which refers to the prediction of white matter lesions using routine medical examinations and complex mathematical algorithms. (9)

From a total population of 1904 adults, 1775 were intentionally selected. Patients taking antidiabetic medications and those with baseline blood glucose levels ≥ 126 mg/dL were excluded.

Baseline determinations included systolic blood pressure (SBP), diastolic blood pressure (DBP), baseline blood glucose levels in mg/dL and glycated hemoglobin (HbA1c).

During the carotid ultrasound procedure, the presence of plaques in the common carotid artery, its bifurcation and, the internal carotid artery was evaluated. Carotid intima-media thickness was measured.

The dependent variable in the CHAID decision tree was the carotid plaque score, assessed by ultrasound and dichotomized into values > 1.20 mm and ≤ 1.20 mm. (10) The carotid plaque score is a measurement used to assess the presence and severity of atherosclerotic plaques in the carotid arteries. This score is obtained by carotid artery ultrasound, which measures the maximum carotid plaque thickness. A value >1.20 mm is associated with increased cardiovascular risk.

Statistical analysis

We used the CHAID decision tree technique, based on a chi-square measurement metric, to segment the data into homogeneous groups and construct a predictive model. This method identifies patterns in the relationship between a dependent variable and multiple independent variables, using both quantitative and categorical data. (11)

CHAID iteratively divides the sample into nodes, creating branches based on the categories of the explanatory variables. In each branch the most significant cut-off points are selected according to the chi-square test, generating mutually exclusive subgroups. (12) For example, in the case of the carotid plaque score the nodes represent differentiated categories according to their association with the variable of interest.

Finally, the terminal node with the strongest strength of association with the root node was selected, which was the presence or absence of carotid plaques > 1.20 mm.

Diagnostic tests were performed to estimate the odds ratio (OR), degree of association (Phi coefficient), sensitivity (S), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), and likelihood ratio (LR). All the statistical calculations were performed using SPSS Statistics 25.0® software package. (13)

Ethical considerations

The database was voluntarily uploaded to Dryad (https://datadryad.org/) under Creative Commons license (CC0). (14) The study was conducted following the recommendations of the Declaration of Helsinki. The database is available at: https://datadryad.org/stash/dataset/doi:10.5061/dryad.73bh2q8.

RESULTS

The characteristics of the selected population are described in Table 1.

Of the 1775 patients, 565 (31.8%) had high-risk carotid plaque score. These patients had significantly higher number of plaques, higher HbA1c and baseline blood glucose levels, and higher systolic and diastolic blood pressure values compared with those without high-risk carotid plaque score ($p < 0.001$). However, there were no significant differences in BMI between both groups ($p = 0.071$). This highlights the association between high-risk carotid plaque score and elevated metabolic and cardiovascular markers (Table 2)

The decision tree with the carotid plaque score as the dependent variable included 2 depth levels and a total of 8 nodes of which 5 were terminal nodes. The tree classified baseline blood glucose levels > 104 mg/dL along with HbA1c values > 6%. as the most decisive variables associated with the presence of high-risk carotid plaques. The main characteristic associated with the absence of high-risk carotid plaque score was the presence of HbA1c values ≤ 5.30% (Figure 1). The association between the presence of baseline blood glucose levels >104 mg/dL and HbA1c >6 % (node 7

Table 1. Baseline characteristics of the population (n=1775)

Variable	
Male sex, n (%)	891 (50.2%)
Age group, n (%)	
18-39 years	164 (9.2%)
40-59 years	838 (47.2%)
≥ 60 years	773 (43.5%)
Carotid plaque score, n (%)	
High risk (> 1.2 mm)	565 (31.8%)
No risk	1210 (68.2%)
Carotid plaque score, median (IQR)	0.40 (0.10-1.00)
Blood glucose levels (mg/dL), mean ± SD	99.86 ± 8.98
HbA1c (%), mean ± SD	5.61± 0.38
BMI (kg/m2), mean ± SD	22.91± 3.28
SBP (mm Hg), mean ± SD	123.14± 18.29
DBP (mm Hg), mean ± SD	73.74± 12.17
Number of plaques, median (IQR)	0 (0-1)
TG (mg/dL), mean ± SD	111.82 ± 69.55
HDL (mg/L), mean ± SD	61.12 ± 15.39

BMI: body mass index; DBP: diastolic blood pressure; HbA1c: glycated hemoglobin; HDL: high-density lipoprotein; IQR: interquartile range; SD: standard deviation; SBP: systolic blood pressure; TG: triglycerides

Table 2. Biological markers in patients with high-risk carotid plaque score

	High risk score (n=565)	No pathological risk score (n=1210)	p
Number of plaques, median (IQR)	2 (0.50-2.50)	0.35 (0.10-1.12)	<0.001
HbA1c (%), mean ± SD	5.67 ± 0.30	5.58 ± 0.29	<0.001
Blood glucose levels (mg/dL), mean ± SD	101.33 ± 9.02	99.22 ± 8.23	<0.001
SBP (mm Hg), mean ± SD	128.64 ± 18.34	120.76 ± 17.72	<0.001
DBP (mm Hg), mean ± SD	75.49 ±12.19	72.98 ± 12.18	<0.001
BMI (kg/m2), mean ± SD	23.13 ± 3.18	22.82 ± 3.26	0.0710

BMI: body mass index; DBP: diastolic blood pressure; HbA1c: glycated hemoglobin; IQR: interquartile range; SBP: systolic blood pressure; SD: standard deviation

of the CHAID decision tree) with carotid plaque score >1.2 mm was moderate (Phi = 0.182). The odds of presenting with high-risk carotid plaque score was 3.69 times higher for patients with elevated blood glucose levels and HbA1c when compared to those with lower blood glucose levels and HbA1c. The sensitivity was low (15%), the specificity high (95%), and the positive and negative predictive values were 61%, and 71%, respectively. The likelihood ratio indicates that patients with blood glucose levels > 104 mg/dL and HbA1c > 6% exhibited a 3.29 times greater probability of a true positive result for high-risk carotid plaque score in comparison to a false positive result (Table 3). Patients with the predominant feature of node 7 of the CHAID decision tree (blood glucose levels > 104 mg/dL and HbA1c > 6%), had a median carotid plaque score of 1.60, while patients in the other nodes had a median carotid plaque score of 0.25 (p = 0.001). In addition, the median number plaques in patients in node 7 was 1.20, while the median number plaques in patients in the other nodes was 0.30 (p < 0.001) (Table 4).

DISCUSSION

The CHAID decision tree classified and divided the continuous variables HbA1c and baseline glucose levels into segments. Baseline blood glucose levels >104 mg/dL and HbA1c >6% were associated with the presence of high-risk carotid plaque score, consistent with prediabetes. This was confirmed with diagnostic tests which demonstrated a significant influence on carotid intima-media thickness, similar to the findings by Zhou et al. (15) The association between HbA1c and carotid plaques has been observed in patients with chronic diseases, as in the studies by Dodos et al. (16) and Cheng et al. (17)

Elevated HbA1c promotes carotid artery atherosclerosis through mechanisms such as the formation

Carotid plaque score		
Node 0		
Category	%	n
High risk (>1.20 mm)	31.80	565
No risk	68.20	1210
Total	100	1775

HbA1c (%) $p < 0.001$

≤ 5.3 | 5.3-6 | >6

Node 1			Node 2			Node 3		
Category	%	n	Category	%	n	Category	%	n
High risk (>1.20 mm)	19.5	59	High risk (>1.20 mm)	31.3	399	High risk (>1.20 mm)	54	107
No risk	80.5	244	No risk	68.7	875	No risk	46	91
Total	17.1	303	Total	71.8	1274	Total	11.2	198

Basal blood glucose, mg/dL $p = 0.035$ Basal blood glucose, mg/dL $p = 0.030$

≤107 | >107 | ≤104 | >104

Node 4			Node 5			Node 6			Node 7		
Category	%	n	Category	%	n	Category	%	n	Category	%	n
High risk (>1.20 mm)	29.7	320	High risk (>1.20 mm)	40.1	79	High risk (>1.20 mm)	37.5	21	High risk (>1.20 mm)	60.6	86
No risk	70.3	757	No risk	59.9	118	No risk	62.5	35	No risk	39.4	56
Total	60.7	1077	Total	11.1	197	Total	3.2	56	Total	8	142

Fig. 1. CHAID decision tree for glycemic profile associated with carotid plaques in non-diabetic adults.

Table 3. Measurements of association between node 7 of the CHAID decision tree and the presence of carotid plaques detected by ultrasound in non-diabetic adults

Phi	0.182
OR (95% CI)	3.69 (2.59-5.28)
S	15%
Sp	95%
PPV	61%
NPV	71%
LR+ (95% CI)	3.29 (2.38-4.54)
LR- (95% CI)	0.89 (0.85-0.93)

LR: likelihood ratio; NPV: negative predictive value; OR: odds ratio; Phi: Phi coefficient; PPV: positive predictive value; S: sensitivity; Sp: specificity

of advanced glycation end-products, oxidative stress and endothelial dysfunction. (18-20) These mechanisms may have an impact on non-diabetic adults who exhibit HbA1c and baseline blood glucose values indicative of prediabetes. suggesting that carotid plaque formation may be a prodromal sign.

The decision tree also identified that HbA1c ≤ 5.30% is associated with absence of high-risk carotid plaques. While these findings suggest an association between HbA1c and the presence of high-risk carotid plaques, further studies and additional evidence are needed to make a strong recommendation for the adoption of HbA1c targets or the routine measurement of HbA1c to prevent cerebrovascular events related to carotid atherosclerosis.

The limitations of this study include the sample size (n=1775), which may not be representative of larger populations, and potential reporting biases due to the retrospective nature of the data collection. In addition, information on other key risk factors, such as dietary habits, physical activity, and family history, which could influence glycemia and atherosclerosis, is lacking. The absence of longitudinal follow-up precludes the establishment of a definitive causal relationship, and the study does not consider individual variability or the use of multiple biomarkers, which could provide a more complete assessment of cardiovascular risk.

CONCLUSIONS

Baseline blood glucose levels >104 mg/dL and HbA1c >6% were associated with the presence of high-risk carotid plaques in non-diabetic adults. Despite the CHAID decision tree excluded triglycerides and HDL as relevant factors, and the observation that baseline blood glucose levels >104 mg/dL and HbA1c levels >6% were associated with a higher prevalence of high-risk carotid plaques in nondiabetic adults, the absence of data on additional potential risk factors, such as total cholesterol or genetics, hinders the inter-

Table 4. Comparison of mean anthropometric, hemodynamic and laboratory tests values according to the presence of baseline blood glucose levels >104 mg/dL and HbA1c >6% in non-diabetic adults (node 7 of the CHAID decision tree).

Variable	Node 7 (n=142)	Nodes 1 to 6 (n= 1633)	p
Carotid plaque score, median (IQR)	1.60 (0.50- 3.70)	0.25 (0.10-0.50)	0.001
Number of plaques, median (IQR)	1.20 (0.80-1.55)	0.30 (0.10-0.50)	< 0.001
BMI (kg/m^2), mean ± SD	24.36 ± 4.18	22.85 ± 3.17	< 0.001
SBP (mm Hg), mean ± SD	127.34 ± 18.64	123.03 ± 18.22	0.007
DBP (mm Hg), mean ± SD	73.65 ± 11.85	73.70 ±12.20	0.962
HbA1c (%), mean ± SD	6.46 ± 0.45	5.59 ± 0.28	<0.001
Blood glucose levels (mg/dL), mean ± SD	114.58 ± 5.86	99.21 ± 8.11	<0.001

BMI: body mass index; DBP: diastolic blood pressure; HbA1c: glycated hemoglobin; IQR: interquartile range; SBP: systolic blood pressure; SD: standard deviation

pretation of these findings. Nevertheless, the routine assessment of HbA1c in nondiabetic adults could be useful in identifying the risk of carotid atherosclerosis, though further research is necessary to ascertain the validity of this association and its implications for disease prevention.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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