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CORRELATION OF CARDIOVASCULAR RISK SCALES WITH CAROTID THICKENING BY B-MODE ULTRASOUND IN PATIENTS WITH HIV

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ABSTRACT

Introduction: HIV promotes atherosclerosis. A marker of atherosclerosis is carotid thickening with B-mode ultrasound. Cardiovascular risk scales are currently available to perform cardiovascular risk screening.
Objective: To determine the correlation of cardiovascular risk scales with carotid thickening by ultrasound B-mode.
Patients and methods: Cross-sectional study of HIV patients undergoing treatment, without comorbidities, with undetectable viral load. Descriptive statistics and inferential analysis, Pearson correlation.
Results: We analyzed 170 patients, 130 men and 40 women. Risk reported by scales: Framingham 2.9%, SCORE 1.4%, Regicor 2.4%, PROCAM 1.9%, and QRISK2 3.3% cardiovascular risk at 10 years. The average thickening of both carotids by B- mode ultrasound was 1.1 mm equivalent to 5.5% risk at 6 years. The correlation coefficient was 0.1 - 0.3.
Conclusions There is no linear correlation between the scales of cardiovascular risk used and the thickening of the carotid intima media.

INTRODUCTION

Several studies suggest an increased frequency of cardiovascular events in population infected with HIV (Klein, Hurley, Quesenberry & Sidney, 2001; Currier, et al., 2003; Triant, Lee, Hadigan & Grinspoon, 2007; Lang, et al., 2010; Durand, Sheehy, Baril, Lelorier & Tremblay, 2011; Chow et al., 2012). Currier et al., (2003), showed that the incidence of coronary heart disease, including myocardial infarction, other ischemic heart disease and coronary atherosclerosis, in patients between 18 and 24 years was generally low, but increased in HIV-infected patients compared to non-infected patients, (RR: 6.76 for men and 2.47 for women). Also, the RR of coronary disease was more important in patients infected with HIV older than 45 years compared with uninfected populations.

Castro et al., (2008) used the risk function of Framingham and determined that the prevalence of cardiovascular risk at 10 years was higher than 10%, similar to patients with HIV infection regardless of the presence of antiretroviral treatment. Likewise, they identified that the main factors associated with the risk were smoking, being male, over 45 years of age and non-HDL cholesterol.

Patients with HIV infection are usually young and therefore have a low risk in the short term and few cardiovascular events, that is why many clinical studies rely on surrogate markers to indirectly assess the burden of cardiovascular disease. Some measurements include intima-media thickness (IMT) and intraluminal arterial plaque evaluated by ultrasound, as well as the evaluation of coronary artery calcification and plaque using computed tomography (CT); these measurements have been moderately associated with coronary atherosclerosis and the risk of future cardiovascular events in population without HIV (Bots et al., 2007). Most studies that measure carotid artery IMT in asymptomatic adults found an increase in the measurements of patients with HIV infection (Hsue et al., 2012).

Among the methods used to evaluate IMT there is B-mode ultrasound, which is a widely used technique for clinical and epidemiological evaluation of atherosclerosis disease of the carotid artery (Chambless et al., 1997). A well-accepted surrogate marker of atherosclerosis is the IMT measurement of the common carotid artery with high resolution B-mode ultrasound. Previous studies have consistently shown that IMT in the common carotid artery is significantly increased in patients with HIV, compared to healthy controls (Maggi et al., 200; Seminari et al., 2002).

Current treatment guidelines recommend that cardiovascular risk should be estimated using a conventional model such as the Framingham score, by means of which Bergersen, Sandvik, Bruun & Tonstad (2004) observed a risk of suffering acute myocardial infarction of 11.9% in HIV patients at 10 years, compared with 5.3% in population without HIV. In Spain, Santos, Palacios, González, Ruiz & Márquez (2005) found a risk of 6.7% in patients with HIV; whereas Castro et al. (2008) detected a higher than 10% prevalence in Mexican patients at 10 years.

On the other hand, the Prospective Cardiovascular Münster Study (PROCAM) function is a simple and accurate tool to calculate the overall risk of myocardial infarction in clinical practice, allowing to guide preventive therapy more accurately (Assmann, Cullen P & Schulte, 2002).

The Data Collection on Adverse Events of Anti-V Drugs - D:A:D is an international collaborative study of 11 cohorts following 33,308 patients infected with type 1 HIV in 212 clinics in Europe, the United States and Australia, and also offers a calculation function of cardiovascular risk (Westring et al., 2010).

Moreover, the Systematic Coronary Risk Evaluation (SCORE) tables are recommended by European societies and the Spanish Interdisciplinary Committee for Cardiovascular Prevention meanwhile the REGICOR (Registre Gironí Cor) function is the only function that has been validated in Spain (Buitrago et al., 2007; Marrugat et al., 2007). The discrepancies between the REGICOR and SCORE scales have been debated (Maiques, 2003), and meanwhile a retrospective cohort study in Spanish urban population for 10 years concluded that SCORE had greater validity than REGICOR in the assessment of the real risk of coronary events and cardiovascular death, no scale was actually adjusted to reality. In fact, REGICOR underestimated the risk, while SCORE overestimated it (Buitrago et al., 2006; Ramos & Marrugat, 2005).

Finally, the QRISK 2 algorithm developed in the United Kingdom uses traditional cardiovascular risk factors such as age, systolic blood pressure, smoking, and the ratio of total cholesterol to HDL. It also includes the use of some antiretrovirals, family history, antihypertensive treatment, and body mass index (Hippisley et al., 2007).

OBJECTIVES

The general purpose of this study was to establish the correlation of cardiovascular risk scales with ultrasound of the carotid artery IMT in patients with HIV infection. Aside, we aimed to ascertain which scale has the greatest association with ultrasonographic results.

METHODS :

We performed a cross - sectional study in patients with HIV infection receiving antiretroviral treatment for more than one year and less than 15 years, with adequate virological control assessed by HIV RNA loads <40 viral copies in 2 determinations made at least 6 months apart. We determined sociodemographic variables of all the patients, time since the diagnosis of HIV infection and exposure to antiretrovirals; the last antiretroviral (current) treatment scheme they were taking, provided that it lasted more than a year with it.

A patient was considered "with cardiovascular risk factors" if they had history of acute myocardial infarction, angina, cerebral vascular disease or peripheral arterial disease. The blood pressure of every participant was measured after they had been sitting for 5 minutes with their feet on the floor and their arms at heart level.

Height was reported in centimeters and weight in kilograms; the body mass index was calculated as the weight in kilograms divided by the square of height. The waist circumference (WC) was measured as the narrowest circumference between the inferior border of the lowest rib and the iliac crest using a non-elastic anthropometric tape. A WC greater than or equal to 94 cm for men and greater than or equal to 80 cm in women is considered a cardiovascular risk factor.

We took 12 ml of venous blood by peripheral venipuncture from which we obtained a serum sample by clot retraction at 37° C for 15 minutes and centrifugation at 800 G for 10 minutes. Total cholesterol (TC), high density lipoprotein (HDL), triglycerides (TG) and low density lipoprotein (LDL), glucose, CD4+ T lymphocyte levels in cells/µL, and viral load in HIV RNA copies/mL were evaluated in each sample.

On the same day that the clinical and biochemical measurements were determined, the measurement of thickening of the carotid intima media was carried out using the protocol adapted from the Cardiovascular Health Study developed by O'Leary et al., 1991. The longitudinal lateral measurement of the distal 10 mm of the left and left common carotid artery, and longitudinal views of the different image planes were obtained (anterior, lateral, and posterior). The mean of the maximum measurement of the nearest and farthest wall for both arteries was used for the final analysis as it has the strongest association with cardiovascular risk factors (O'Leary & Polak, 2002). The measurement was performed with a Philips ATL ultrasound equipment, model HDI 3500, using B-mode with a high frequency linear transducer between 5 to 12 MHz, making measurements in both transversal and longitudinal sections in the carotid segments of the distal third of the common carotid and bifurcation carotid. We analyzed the highest diameter measured in millimeters of thickness, and defined as thickening the one with a value of 1 mm or greater. The cardiovascular risk was calculated directly from the official electronic pages of the corresponding societies: Framingham, PROCAM, SCORE, REGICOR and QRISK2.

The current antiretroviral treatment had to include a non-nucleoside reverse transcriptase inhibitor, a protease inhibitor or an integrase inhibitor, as well as the combination of two nucleoside analogues as a backbone.

The exclusion criteria were patients under 18 years old, pregnant women, patients without antiretroviral treatment or without virological control, with history of previous cardiovascular events (myocardial infarction, cerebral vascular disease or peripheral arterial vascular disease), with diabetes mellitus, previously or currently smoking, and hypertension or dyslipidemia at the time of the study.

We performed descriptive statistics with measures of central tendency and inferential analysis with Kendall's tau and Pearson correlation.

This study was approved by the local committee of Ethics and Research of the Mexican Institute of Social Security.

RESULTS

We studied 170 patients (130 men and 40 women) who agreed to be part of the investigation, and who met the selection criteria. The mean age of the patients was 43.7 years, the average weight was 71.7 kilograms, the average height was 166 centimeters and the average WC was 90.5 centimeters, meanwhile the average CD4 + T lymphocytes was 582.

The thickening of the carotid arteries was on average 1 mm in the right common carotid and 1.1 mm in the right bulb, the right internal carotid was 1 mm. On the left side the common carotid was 1 mm, 1.1 mm in the bulb and the left internal carotid had 1 mm. The average of both right and left carotid arteries added together is 1.1 millimeters.

Regarding the cardiovascular risk scales, the average values were as follows: Framingham of 2.9, which means a 3 % cardiovascular risk at 10 years; SCORE of 1.4, with a 1% risk of fatal cardiovascular disease at 10 years; Regicor of 2.4, meaning 2.4% risk of coronary event (angina, myocardial infarction with or without symptoms, mortal or not) at 10 years; PROCAM of 1.9, with a 1% risk of acute coronary event at 10 years; and QRISK2 of 3.3, that is 3.3% risk of infarction or cerebral vascular disease at 10 years.

The average of blood pressure and the rest of results obtained from the blood samples are described within Table 1.

Table 1. Average results

	Average
Systolic TA	116.5
Diastolic TA	73.7
Cholesterol md / dl	182.8
Triglycerides mg / dl	269.1
HDL mg / dl	41.4
LDL mg / dl	89.1
VLDL mg / dl	61.5
Glucose mg / dl	98.6

When we performed the correlation analysis of the cardiovascular risk scales with the thickening of the right and left carotid intima media, we found minimal correlation values, meaning there is no linear relationship (Table 2 and Table 3).

Table 2. Correlation of cardiovascular risk scales with ultrasound of the carotid IMT on the right side in patients with HIV

	USG of Carotid IMT on the right side					
	Common Carotid		Bulb		Internal Carotid	
	R	p	*R*	p	*R*	p
Framingham	0.036	> 0.05	0.124	> 0.05	0.190	> 0.05
SCORE	0.221	<0.001	0.148	<0.05	0.221	<0.001
Regicor	0.251	<0.05	0.202	<0.05	0.141	<0.05
PROCAM	0.132	<0.001	0.192	<0.001	0.184	<0.05
QRISK2	0.363	<0.001	0.184	<0.001	0.179	<0.05

Statistical Analysis: Pearson's R (Somers' d)/Tested with Kendall's tau

Source: SPSS 21

Table 3. Correlation of cardiovascular risk scales with ultrasound of the carotid IMT on the left side in patients with HIV

	USG of Carotid IMT on the left side					
	Common Carotid		Bulb		Internal Carotid	
	R	p	*R*	p	*R*	p
Framingham	0.001	> 0.05	0.330	> 0.05	0.015	> 0.05
SCORE	0.183	<0.001	0.207	<0.001	0.145	<0.05
Regicor	0.211	<0.001	0.217	<0.001	0.050	> 0.05
PROCAM	0.207	<0.001	0.217	<0.001	0.152	<0.05
QRISK2	.239	<0.05	0.218	<0.001	0.100	> 0.05

Statistical Analysis: Pearson's R (Somers' d)/Tested with Kendall's tau
Source: SPSS 21

DISCUSSION

The need to provide timely primary and secondary interventions in patients with cardiovascular disease has led to the development and use of tools or risk calculators to guide research and management to populations with more risk factors. Although some risk calculators have shown they can predict cardiovascular outcomes in the general population with reasonable certainty, it has been observed that the accuracy differs depending on the tool and on the population. In people infected with HIV these tools have underestimated the presence of subclinical atherosclerosis nor can predict the frequency of myocardial infarction.

In our study, we selected patients in such a way that there were few confounding factors that could modify the interpretation. In order to achieve this we excluded smokers, people with known cardiovascular risk factors, pathologies that created cardiovascular outcomes whether or not they were under treatment, and people with uncontrolled viremia. That left to study only the population that strictly did not have cardiovascular risk factors other than HIV infection and antiretroviral treatment.

We found that even though there was some carotid thickening while making the average of measurements, and particularly at the level of the bilateral bulb, the average result of 1.1 mm indicates that the incidence of cardiovascular events would be 5.5% at 6 years (Chain, Lucierdi, Feldman & Valberdi, 2005).

The debate goes on about the role of screening and early management of cardiovascular risk, especially towards the type and time of screening. So far no study has shown that the use of the aforementioned tools has an advantage in the management of cardiovascular outcome. In our studied population, which was heterogeneous with prolonged antiretroviral treatment and under different treatment schemes, the screening with the B-mode ultrasound of the carotid IMT reported a low cardiovascular risk, as well as the risk assessment scales, and yet there was no linear mathematical correlation (Nadel & Holloway, 2017).

Because this was a relatively young population and each case should be analyzed in a particular way due to their individual risk factors, it is not clear which one is the best method to scrutinize them and treat the ones at high risk. Even a non-invasive and relatively accessible method such as B-mode ultrasound showed a low risk at 6 years in our patients. There's a need to perform studies on this population with unique characteristics that include risk factors and a greater number of patients in different strata, as well as a prolonged follow-up that provides more evidence about the best screening method and early intervention.

CONCLUSIONS

In our strictly selected study population with cardiovascular risk factors only associated with HIV infection and with antiretroviral treatment, we found that there is a low cardiovascular risk according to the measurement by thickening of the carotid intima media measured with B-mode ultrasound, reporting a thickening average of both carotids of 1.1 mm, equivalent to 5.5% of risk at 6 years. According to the risk tools we evaluated, the estimated risk resulted as 3% for Framingham and QRISK2, 2.4% for Regicor, and 1% for SCORE and PROCAM scales at 10 years of a cardiovascular outcome. There is no linear correlation between the employed cardiovascular risk scales and the results of thickening of the carotid intima media.

In our study, because we analyzed a relatively young population with few cardiovascular risk factors, it was not possible to determine which is the best method to screen this population or if there is an association between the risk calculators and the validated measurement method of carotid IMT. It is necessary to perform a longitudinal research including patients with different risk strata and with a greater number of people in this population with such unique characteristics.

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