Frequency of metabolic syndrome and stratification of cardiovascular risk in patients with HIV by using three scoring systems

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Abstract

Introduction: The presence of metabolic syndrome and cardiovascular risk in HIV positive patients has been overlooked in patients with HIV infection.

Objectives: To evaluate the frequency of metabolic syndrome and compare cardiovascular risk stratification according to the Framingham, PROCAM, and SCORE equations in HIV patients.

Methodology: A cross-sectional study of 760 HIV-infected adults from January 2016 to December 2018. The presence of metabolic syndrome was assessed using the ATP-III criteria, and the cardiovascular risk score was examined.

Results: The most frequent comorbidities were smoking, hypercholesterolemia, and high blood pressure. Student's T test was carried out, showing differences in the classification of low to moderate risk. The number of HIV-infected male patients identified as having moderate cardiovascular risk according to the Framingham risk equation was two folds compared to those with the PROCAM and SCORE systems.

Conclusions: This study showed a high prevalence of patients with low cardiovascular risk. It is appropriate to consider cardiovascular risk factors in patients with HIV, since they are very frequently associated with adverse outcomes of this type.

Keywords: HIV; risk factors; mortality; prevalence.

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Frecuencia del síndrome metabólico y estratificación del riesgo cardiovascular en pacientes con VIH mediante tres sistemas de puntuación

Resumen

Introducción: La presencia del síndrome metabólico y el riesgo cardiovascular en pacientes VIH positivos ha sido desestimado en pacientes con infección por VIH.

Objetivos: Evaluar la frecuencia del síndrome metabólico y comparar la estratificación del riesgo cardiovascular según las ecuaciones de Framingham, PROCAM y SCORE en pacientes con VIH.

Metodología: estudio transversal de 760 adultos infectados por el VIH en el periodo enero de 2016-diciembre de 2018. Se evaluó la presencia de síndrome metabólico a través de los criterios del ATP-III y se examinó la puntuación de riesgo cardiovascular.

Resultados: Las comorbilidades más frecuentes fueron el tabaquismo, la hipercolesterolemia y la hipertensión arterial. Se realizó la prueba T de Student, y a partir de ella se lograron apreciar diferencias en categorización de riesgo bajo a moderado. El número de pacientes varones infectados por el VIH identificados como de riesgo cardiovascular moderado según la ecuación de riesgo de Framingham fue mayor del doble en comparación con los sistemas PROCAM y SCORE.

Conclusiones: El estudio mostró una alta prevalencia de pacientes con bajo riesgo cardiovascular. Es pertinente considerar los factores de riesgo cardiovascular en pacientes con VIH, ya que estos se encuentran frecuentemente asociados con desenlaces adversos de este tipo.

Palabras clave: VIH; factores de riesgo; mortalidad; prevalencia.

Frequência da síndrome metabólica e estratificação do risco cardiovascular em pacientes HIV-positivos usando três sistemas de pontuação

Resumo

Introdução: A presença da síndrome metabólica e do risco cardiovascular em pacientes HIV positivos tem sido negligenciada em pacientes com infecção por HIV.

Objetivos: Avaliar a frequência da síndrome metabólica e comparar a estratificação do risco cardiovascular de acordo com as equações de Framingham, PROCAM e SCORE em pacientes com HIV.

Metodologia: estudo transversal de 760 adultos infectados com HIV no período de Janeiro de 2016-Dezembro de 2018. A presença de síndrome metabólica foi avaliada através de critérios ATP-III e a pontuação de risco cardiovascular foi examinada.

Resultados: As comorbilidades mais frequentes foram o tabagismo, a hipercolesterolêmia e a hipertensão. Realizou-se o teste T Student, e a partir dele foram apreciadas as diferenças de categorização de risco baixo a moderado. O número de pacientes masculinos infectados com HIV identificados como de risco cardiovascular moderado de acordo com a equação de risco de Framingham foi mais do dobro em comparação com o PROCAM e SCORE.

Conclusões: O estudo mostrou uma elevada prevalência de pacientes com baixo risco cardiovascular. É pertinente considerar fatores de risco cardiovascular em pacientes com HIV, uma vez que estes estão frequentemente associados a resultados cardiovasculares adversos.

Palavras-chave: HIV; fatores de risco; mortalidade; prevalência.

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INTRODUCTION

Antiretroviral therapy has changed the natural history of HIV infection, leading to a significant decrease in morbidity and mortality and a marked prolongation of life expectancy. However, the epidemiologic overlapping between patients with HIV infection and those at risk of cardiovascular disease has increased. In this regard, the weight of evidence from prospective, observational, and surrogate studies suggests that highly effective antiretroviral therapy may be associated with an increased risk of future cardiovascular events, and it may be related to dyslipidemia and other metabolic abnormalities found in HIV patients (1).

Since the identification and management of cardiovascular risk factors in HIV-infected adults have become urgent issues, the Pavia Consensus Statement (2) and the guidelines of the AIDS Clinical Trials Group of the Society of Infectious Diseases of America/Adults (3) for the assessment and management of dyslipidemia, based on the Adult Treatment Panel (ATP) III of the National Cholesterol Education Program (NCEP) (4), recommend target lipid levels and treatment of dyslipidemia in patients with HIV infection according to the overall cardiovascular risk estimated by the Framingham risk calculation.

It should be noted that, based on the initial Framingham plots adapted by Anderson et al. (5), other similar but modified systems have been proposed (6-8). Thus, the NCEP-ATP III risk factor score is derived from an update of the Framingham database and the methodology reported by Wilson et al. (8). Given that the Framingham equation clearly overestimates absolute risk in populations with lower rates of coronary disease, alternative risk systems have been developed (9-12). Although several studies have focused on the prevalence of cardiovascular risk factors in HIV-infected populations (13-16), few have evaluated the coronary risk score and have always based on the Framingham risk scoring system (17- 19), there is incomplete data on HIV-infected patients and, for instance, there is a lack of comparative studies on coronary heart disease risk factor scoring. Therefore, the study of the global cardiovascular risk score in this specific population is justified, especially to compare the cardiovascular risk estimated at ten years by the Framingham equation, according to the NCEP-ATP III guidelines, algorithm 4 of the Prospective Cardiovascular Münster (PROCAM) (20), and the Systematic Evaluation of Coronary Risk (SCORE), recommended by the Third Joint European Task Force (21,22).

MATERIALS AND METHODS

Study Population

The patients were part 'of a cross-cutting cohort of HIV infected adults, for whom cardiovascular

risk factor was assessed by using three validated scoring systems. All of them had total cholesterol tests carried out while fasted, as well as high-density lipoprotein cholesterol (HDL), triglycerides and plasma glucose.

Cardiovascular Risk Assessment

The frequency and factors of the metabolic syndrome were analyzed using the ATP-III criteria. Cardiovascular risk was estimated for each subject by using the three risk equations, and subjects were then classified as those with low, moderate, or high coronary risk at 10 years using Framingham (<10%, 10-20%, and >20%, respectively) and SCORE (<3%, 3-4% and ≥5%, respectively) (21). Patients with established coronary disease or other atherosclerotic diseases were directly defined as being at high cardiovascular risk (>20%) according to the three guidelines (4,20,21). The same occurred with those in primary prevention with type 2 diabetes mellitus when the Framingham and SCORE systems were used (21). On the other hand, the risk score was calculated in HIV-infected patients with risk factors from 0 to 1 in primary prevention, in whom risk assessment was unnecessary when the NCEP-ATP III guidelines were applied (4). For the SCORE system, the 10-year graph calculated the risk of fatal cardiovascular disease by gender, age, systolic blood pressure, smoking, and total cholesterol/HDL cholesterol ratio (21).

Statistical Analysis

Quantitative variables are shown as mean ± standard deviation or median (interquartile range) according to their distribution, and qualitative variables as percentages with 95% confidence intervals (CI). Student's t-test was performed to evaluate the differences between the measurements and the chi-square test (χ^2) in order to verify the degree of association of the categorical variables. A value of $p < 0.05$ was considered statistically significant. Cohen's kappa coefficient, which is a statistical measure that adjusts the effect of chance in the proportion of correspondence observed for qualitative elements (categorical variables), was used to estimate the correspondence between the three risk equations mentioned. All statistical analyzes of the database results were made with the Statistical Package for Social Sciences (SPSS for Windows, version 22.1).

Ethical Considerations

The ethical aspects of this research work were set based on the Belmont Report criteria, adjusted to its principles of respect for the person, beneficence and justice, and the Declaration of Helsinki of the World Medical Association of 1964. Also, it is subject to the Venezuelan legislation and its Code of Medical Ethics of 1985 (currently in force), in its title V, chapter 4, in relation to research on human beings.

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The highest standards were maintained, which allowed the protection of the privacy and physical integrity of the participating subjects. The objectives of this research were explained through an informed consent, which contained the procedures for inherent complications and risks in detail and in a clear and understandable language.

RESULTS

Among the 760 HIV-infected patients, 89 of them (11.7%: CI95%: 9.5-14.2) were previously unaware of their diagnosis, 53 of them were unaware of their diagnosis (7.0%; CI95%: 5, 3-9.0). Among the latter, 230 (30.3%; 95% CI: 27.0-33.7) were on protease inhibitor-based therapy. The mean known duration of HIV infection was 107 (67-153) months, and 248 (32.6%; 95% CI: 29.3-36.1) of the patients had category C HIV disease. The median CD4 cell count was 481 (305-691) × 106 cells/L, and 63% of patients (95% CI: 59.3-66.3) had viral loads less than 500 copies per milliliter. Among the history, 108 (14.3%; 95% CI: 11.8-16.9) had premature coronary disease, 508 (66.8%; 95% CI: 63.4-70.2) were smokers, and 33 (4.3%; 95% CI: 3.0-6.0) had type 2 diabetes (Table 1).

The male gender was the most frequently affected, with 52% of the total number of patients. The presence of hypercholesterolemia was the main criterion for metabolic syndrome (52%), followed

Table 1. ATP-III criteria applied to the study patient population

ATP-III Criteria	Multivariate Analysis (%)
BMI	
High	27
Normal	73
Blood pressure	
High	32
Normal	68
Abdominal circumference	
High	24
Normal	76
Glycemia	
High	4,3
Normal	95,7
Total cholesterol	
High	52
Normal	48
High-density lipoproteins	
Low	28
Normal	72
Triglycerides	
High	19
Normal	81
Gender	
Male	59
Female	41

by arterial hypertension (32%), low concentrations of HDL (28%), a high body mass index (27%), a high abdominal circumference (24%), high triglycerides (19%), and diabetes mellitus or abnormal blood glucose (4.3%).

Cardiovascular risk assessment was not applied in the 25 patients with established cardiovascular disease (3.4 %; 95 % CI: 2.1-4.8), and all of them were directly assigned to the high-risk category of the three systems. The prevalence of patients with low, moderate, and high cardiovascular risk, according to the Framingham, PROCAM, and SCORE equations, is shown in table 2.

When performing the kappa test, we observed that the correspondence between these three risk functions was significant, but overall moderate (Framingham and PROCAM: $\kappa = 0.48$ and $p < 0.0001$; Framingham and SCORE: $\kappa = 0.32$ and $p < 0.0001$, PROCAM and SCORE: $\kappa = 0.49$ and $p < 0.0001$).

Table 2. Prevalence of HIV-infected patients with low, moderate and high cardiovascular risk according to Framingham (<10 %, 10-20 % and >20 %), SCORE (<3 %, 3-4 % and ≥5 %), and PROCAM (<10 %, 10-20 % and >20 %)

Risk	Low (%)	Moderate (%)	High (%)
Framingham	76.6	15.1	8.3
SCORE	88.6	3.0	8.4
PROCAM	90.1	4.9	5.0

The Framingham equation classified a higher percentage of HIV-infected male patients with moderate cardiovascular risk and a lower percentage with low risk, compared to the PROCAM and SCORE equations, being statistically significant in both cases ($p < 0.0001$) (Table 3).

Table 3. Prevalence of HIV-infected patients classified as low, moderate and high cardiovascular risk according to gender and according to Framingham. (<10 %, 10-20 % and >20 %, respectively), SCORE (<3 %, 3-4 % and ≥5 %, respectively). and PROCAM (<10 %, 10-20 % and >20 %, respectively)

Variables	Men Low risk	Women Low risk	Men Moderate risk	Women Moderate risk	Men High risk	Women High risk
Framingham	386 (70.2 %)	196 (93.3 %)	110 (20 %)	5 (2.4 %)	54 (9.8 %)	9 (4.3 %)
	[66.2-73.9]*	[89.1-96.3]*	[16.7-23.6]*	[0.7-5.5]*	[7.5-12.6]*	[1.9-7.9]*
SCORE	482 (87.6 %)*	191 (90.9 %)*	17 (3.1 %)	6 (2.9 %)	51 (9.3 %)	13 (6.2 %)
	[84.6-90.3]*	[86.2-94.5]*	[1.8-4.9]*	[1.1-6.1]*	[6.9-12.0]*	[3.3-10.4]*
PROCAM	488 (88.7 %)	197 (93.8 %)	28 (5.1 %)	9 (4.3 %)	34 (6.2 %)	4 (1.9 %)
	[85.8-91.2]*	[89.6-96.7]*	[3.4-7.3]*	[2.0-8.0]*	[4.3-8.5]*	[0.5-4.8]*

* Chi square = $p < 0.05$.

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To evaluate the differences in the classification of patients with moderate-high cardiovascular risk according to the scale system applied, patients with moderate-high risk estimated by each risk equation were selected, and then the risk was re-calculated with the other two systems. Of the patients classified in moderate-high risk by the Framingham equation, 53% were assigned to the low-risk category when SCORE was applied, and 61% with PROCAM. However, the Framingham equation only reclassified 6% of the patients in low cardiovascular risk who had been classified by the PROCAM or SCORE systems in moderate-high risk. (Table 4).

Table 4. Differences between the three risk systems when assessing cardiovascular risk in HIV-infected patients with moderate-high risk

Scores	Framingham n = 178	SCORE n = 88	PROCAM n = 75
Framingham			
Low (n [%])	—	5 (5.7)	6 (6.6)
Moderate (n [%])	115 (64.6)	25 (28.4)	25 (33.3)
High (n [%])	63 (35.4)	58 (65.9)	44 (58.7)
SCORE			
Low (n [%])	95 (53.4)	—	17 (22.7)
Moderate (n [%])	23 (12.9)	28 (31.8)	15 (20)
High (n [%])	60 (33.7)	60 (68.2)	43 (57.3)
PROCAM			
Low (n [%])	109 (61.2)	30 (34.1)	—
Moderate (n [%])	32 (18)	21 (23.9)	37 (49.3)
High (n [%])	37 (20.8)	37 (42)	38 (50.7)

With the Student's t-test, it was possible to appreciate differences in the classification of low to moderate risk. In this regard, the number of HIV-infected male patients identified as having moderate cardiovascular risk, according to the Framingham risk equation, was more than double compared to the PROCAM and SCORE systems.

DISCUSSION

Global risk assessment has become an accepted component of clinical guidelines and recommendations in cardiovascular medicine. Thus, the different global cardiovascular risk estimation scales are useful for identifying patients "at risk". This study showed a high prevalence of HIV-infected patients with low cardiovascular risk, regardless of the coronary risk assessment system used. Although this study does not include any control group of uninfected subjects, the few studies that analyze cardiovascular risk score found higher levels of cardiovascular risk compared to the general population (14,17,18). When comparing the findings of this research with those of the study of data collection on adverse events of anti-HIV drugs (19), a significant difference was found between those who presented a cardiac risk greater than 10% (23.4% vs 9.0%, respectively); but somewhat lower than that described by the study by Hadigan et al. (17) (23.4% vs 29.1%, respectively).

In the latter, the use of the Framingham risk score by Wilson et al. (8), based on the blood pressure and cholesterol categories proposed by the JNC-V (23) and NCEP-ATP II (24), could explain this slight discrepancy. The same occurred when comparing the prevalence of HIV-infected patients with a 10-year coronary risk greater than 20 % in this study with that of the Norwegian study (18). There was correspondence of 83.4% to 92.6% in cardiovascular risk classification among those who used Framingham, PROCAM, and SCORE equations. The discordance arose from differences in the classification of low to moderate risk.

Accordingly, the number of HIV-infected male patients identified as having moderate cardiovascular risk, according to the Framingham risk equation, was four times higher compared to the PROCAM and SCORE systems. The genetic background and extensive racial admixture of the present HIV cohort could support the well-known absolute overestimate of cardiovascular risk (9,10); an overestimate that was also observed when the PROCAM system was applied to subjects from the Prospective Epidemiological Study of Myocardial Infarction (12).

To this end, it has been noted that Mediterranean populations have protective factors, such as their diets and other lifestyle habits, which reduce their risk of coronary heart disease to lower levels than those observed in populations further north in Europe (25) for each risk factor or each combination of risk factors, while the effects on large population groups in Latin America are unknown. This study shows that the best correspondence is found between the PROCAM and SCORE systems.

On the other hand, leaving aside comparisons of risk equations, the different scales for the estimation of global cardiovascular risk in the general population could underestimate the real risk if HIV-specific factors, such as altered immunity, exposure to CART or onset of lipodystrophy, which may play a part in the acceleration of atherosclerosis. In this sense, Law et al. (19) reported that the Framingham equation slightly underestimates the risk of myocardial infarction in subjects from the DAD trial who received antiretroviral therapy.

CONCLUSION

This study showed that the presence of metabolic syndrome criteria in HIV-diagnosed patients is really high. The estimate of cardiovascular risk in this particular group may be underestimated. There was a high frequency of patients who smoked, which is the main modifiable risk factor in the study population, at 66.8 %. The presence of hypercholesterolemia was the main criterion for metabolic syndrome (52 %), followed by arterial hypertension in (32 %), and low concentrations of HDL (28 %). These figures are concerning

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since they differ from those found in the general population.

This study emphasizes the need to validate the different risk equations used to assess cardiovascular risk in HIV-infected patients, taking into account the new related parameters. Although obtaining and maintaining virological control is the primary goal in patients with HIV infection, cardiovascular risk assessment should not be underestimated in this population during their aging process.

We encourage research groups in Latin America and other latitudes to better estimate the populations diagnosed with HIV, since other variables that have not been validated in this particular group of patients and that may contribute to decrease the burden of cardiovascular disease may arise over time, as well as the adverse outcomes that have currently changed the epidemiological landscape of these patients with the introduction of highly effective antiretroviral therapy, to the point that opportunistic infections have been left in second place; and now, ischemic heart disease and cerebrovascular disease are the ones causing the most mortality and sequelae in these patients.

CONFLICT OF INTEREST

The authors of this research state having no conflict of interest.

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