Antirretroviral therapy effect in the intima-medio complex and ankle-brachial index in patients infected by HIV

Efeito da terapia antirretroviral e dos níveis de carga viral no complexo médio-intimal e no índice tornozelo-braço em pacientes infectados pelo HIV

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Abstract

Objectives: To precociously identify the prevalence of atherosclerosis caused by thickening of the intima-media complex of the common carotid arteries and of the ankle brachial index. These measurements were associated with the classical risk factors of atherosclerosis and the specific factors of those infected by HIV (duration of disease, length of treatment, kind of treatment, kind of antiretroviral therapy used, CD4 and viral load).
Methods: Seventy cases infected by HIV were assessed by automatic measurement of the intima-media complex in the carotids and of the ankle brachial index. The classical risk factors of atherosclerosis (age, gender, systemic arterial hypertension, smoking, hypercholesterolemia, hypertriglyceridemia, obesity, and family history of cardiovascular events), anthropometric measurements and the variables related to HIV were taken into consideration. The adopted level of significance was 5%.
Results: The mean time of HIV diagnosis was 104.9 months, mean duration of treatment was 97.9 months. As regard to the type of treatment, 47 (67.1%) used protease inhibitor for more than six months and 36 (51.4%) are using it recently. The ankle brachial index was increased in one patient (0.7%), and the intima-media complex was not thickened in any individual. There was no significant association of the measurement of the intima-media complex of the right common carotid with any of the variables analyzed.
Conclusions: Young individuals under the use of antiretroviral therapy for five years or more did not show increase in thickness of the intima-media complex or increase in the ankle brachial index, and there was no difference in the intima-media complex thickness associated with the therapeutical scheme of antiretroviral used or the viral load level.

Keywords: atherosclerosis; ankle brachial index; anti-retroviral agent.

Resumo

Objetivos: Identificar precocemente a prevalência de aterosclerose, por causa do espessamento do complexo médio-intimal das carótidas comuns e do índice tornozelo-braço. Essas medidas foram relacionadas com os fatores de risco clássicos de aterosclerose e os específicos dos infectados pelo HIV (tempo de doença, tempo de tratamento, tipo de tratamento, tipo de terapia antirretroviral utilizada, CD4 e carga viral).
Métodos: Setenta casos infectados com o HIV foram avaliados pela medida automática do complexo médio-intimal nas carótidas e do índice tornozelo-braço. Consideraram-se os fatores de risco clássicos de aterosclerose (idade, sexo, hipertensão arterial sistêmica, tabagismo, hipercolesterolemia, hipertrigliceridemia, obesidade e história familiar de evento cardiovascular), as medidas antropométricas e as variáveis relacionadas ao HIV. O nível de significância assumido foi de 5%.
Resultados: O tempo médio de diagnóstico do HIV foi de 104,9 meses e de tratamento foi de 97,9 meses. Quanto ao tipo de tratamento, 47 (67,1%) fizeram uso de inibidor de protease por mais de seis meses e 36 (51,4%) estão em uso atualmente. O índice tornozelo-braço estava aumentado em

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um único paciente (0,7%) e não se evidenciou espessamento do complexo médio-intimal em nenhum indivíduo. Não existiu associação significante da medida do complexo médio-intimal da carótida comum direita com nenhuma das variáveis analisadas.
Conclusões: Indivíduos jovens, sob o uso de terapia antirretroviral por cinco anos ou mais, não apresentaram espessamento do complexo médio-intimal ou aumento do índice tornozelo-braço. Não houve diferença do espessamento do complexo médio-intimal associada ao tipo de esquema antirretroviral utilizado ou nível de carga viral.

Palavras-chave: aterosclerose; índice tornozelo-braço; anti-retrovirais.

Introduction

Individuals infected by the human immunodeficiency virus (HIV) have a different life condition than non-infected individuals, regarding morbidity and mortality due to early atherosclerosis and associated cardiovascular events[1-4].

Atherosclerosis is one of the major causes of morbidity and mortality in the world. Its effect on lowering expectancy is especially caused by acute myocardial infarction (AMI) and stroke[5,6].

Ultrasonography allows the identification of changes in the arterial wall , as well as the the evaluation of atherosclerotic disease progression and response to treatment[7]. Changes in the arterial wall are insidious and precede clinical events, which are a consequence of advanced atherosclerotic disease. Early arterial changes can be seen at B-mode ultrasonography by the evaluation and measurement of the intima-media complex (IMC)[8,9]. It has been used in epidemiological and cardiac risk stratification studies as a subclinical marker of atherosclerosis. It may work as an important predictor of morbid events, and the main advantage of this method is its reproducibility [7,10,11].

The potent antiretroviral therapy (ARVT) improved the quality and increased life expectancy of patients infected by HIV[12-15]. However, this therapy has been associated with a variety of proatherogenic adverse effects, with consequences that can be fatal[3,16-19]. The increased mortality due to cardiovascular events in young patients with HIV, who many times do not presented the classic risk factors for atherosclerosis, is a concern and object of recent studies[1-3,20]. The genesis of atherosclerosis in these individuals is not completely clear. Some authors suggest that the medication class, called protease inhibitors (PI), can be associated with early atherosclerosis and cardiovascular events[4,21,22]. The actual role of ARVT and HIV in the increased risk of cardiovascular disease is not clear. Possible triggering factors are: the proinflammatory state determined by the viral infection; the direct or metabolic-mediated effects triggered by antiretroviral agents (ARVA), especially PIs; the immunodeficiency state, or even the association of these factors.

Among the ARVA, PIs are more commonly associated with dyslipidemia and insulin resistance, even though medication from other classes – such as nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) and non-nucleoside/nucleotide reverse transcriptase inhibitors (NNRTI) – can be involved in metabolic disorders and acute coronary events. PIs, and, less importantly, NRTI, seem to be involved in the direct metabolic effects, and indirectly involved in lipodystrophy[21-25].

The IMC can be used as a predictor of atherosclerotic disease in coronary arteries, regardless of the classic risk factors: age, gender, arterial hypertension (AH), dyslipidemia, diabetes and family history of coronary artery disease (CAD)[8,26-28]. The IMC measurement has also been performed with patients with HIV/AIDS as an early marker to investigate risk factors for atherosclerosis, thus attempting to evaluate specific factors that are related to the infection and to therapy[29-32].

The ankle-brachial index (ABI) is a non-invasive method with high predictive value for peripheral arterial disease, and it is significantly associated with the risk of cardiovascular mortality; its cost is low, and it has been validated in the general population[15,33]. Reduction of ABI to values lower than 0.9 is associated with the significant increase in cardiovascular risk, especially by AMI and stroke, independently of other risk factors[34,35]. Increase in the ABI (≥1.3) is mostly due to changes in arterial compliance rather than stenosis, which would be responsible for decreasing the ABI. The prevalence of high ABI in patients with HIV can be mediated by changes in vascular wall elasticity, as well as by the formation of atheromatous plaques[15].

Considering that the early detection of atherosclerosis in individuals with HIV/AIDS would allow early treatment of patients who had a higher risk of developing cardiovascular events, the current study had the objective of determining early prevalence and the analysis of atherosclerosis, by measuring the thickening of the common carotid IMC and the ABI. These measurements were then related to the classic atherosclerosis risk factors and to specific factors of those infected by HIV (time of disease, time of treatment,

type of antiretroviral treatment and type of antiretroviral therapy used).

Methods

This is a prospective, observational, analytical, cross-sectional and comparative study. Seventy adult subjects, enrolled in the Program of Prevention, Control and Treatment of AIDS at the *Hospital das Clínicas* of *Universidade Federal de Pernambuco* (UFPE), were consecutively selected at a routine visit to the clinic. The subjects were up to 50 years old. Data were collected from August to October 2009. The subjects had been on ARVT for at least five years and had no history of diabetes or cardiovascular diseases – angina pectoris, AMI, stroke or peripheral arterial disease (PAD), nor had been admitted to the hospital in the past two months.

All patients signed the informed consent form. The project was approved by the UFPE Research Ethics Committee. The data collection protocol consisted of a clinical questionnaire. Ultrasonography and the ABI measurement were performed by a researcher "blinded" to the clinical information of patients.

Participants of this study were questioned as to classic risk factors for atherosclerosis: AH, smoking, hypercholesterolemia, hypertriglyceridemia, and family history of cardiovascular events – AMI, angina, stroke and peripheral arterial disease (PAD). For the evaluation of obesity, the body mass index (BMI) and abdominal circumference (AC) were measured[36,37].

Ultrasound evaluation of the carotid IMC was performed on the B-mode of the compact Vivid *i* equipment (General Electric®), with a linear probe (4–10 mHz). The common carotid artery was evaluated just proximal to its bifurcation, and the internal carotid in its first 2 cm. The exams were bilateral. IMC was measured in a plaque-free site at the posterior wall of the carotids and defined as the distance between the two echogenic lines represented by the lumen-intima interface and the media-adventitia of the arterial wall. IMC automatic measurement was performed in the right and left common carotid arteries with a software that determines the average, maximum and minimum measurements (Figure 1). In the same site, three manual measurements were taken, which allowed calculating the arithmetic mean of the manual measurement of the right and left common carotid arteries, as well as the maximum and minimum measurements (Figure 2). The internal right and left carotid arteries were manually measured. The mean of the automatic measurement of the right common carotid (RCC) was defined as the gold standard[8,38]. Since the studied population was aged up to 50 years, IMG was considered thickened when it measured >0.8 mm[39]. The presence of a plaque was defined when the IMC thickness was >1.5 mm[8,40].

ABI was calculated after measuring the arterial blood pressure in the right and left ankles, which was performed under ulsonographic viewing of the arteries. To measure the blood pressure in the upper (UL) and lower limbs (LL), a Becton Dickinson® sphygmomanometer and a compact color Doppler of GE, Vivid *i* model were used. Segmental evaluation of the posterior tibial and dorsalis pedis arteries was performed with Doppler ultrasonography, and all patients presented triphasic arterial flow. Systolic blood pressure was measured in the posterior tibial arteries at the ankle. ABI was calculated by dividing the ankle systolic pressure by the higher brachial systolic pressure. ABI value from 0.9 to 1.3 was considered normal; >1.3, incompressible arteries; and <0.9, the presence of PAD[34,35].

In order to assess the reproducibility of the method, the IMC of the carotid arteries of 20 patients was measured by two independent observers.

Definition of the variables related to HIV

The studied variables that were correlated with the mean IMC measurement in the RCC were: time from diagnosis of HIV, duration of treatment with ARV, use of ARV with PI, irregular use of ARV, use of PI for more than six months, current class of ARVT, type of current ARVT scheme, current viral load (VL), highest VL, recent CD4 count, lowest CD4 count and number of used schemes. The time from HIV diagnosis was measured in months, and since all of the patients had been diagnosed for at least 60 months, the time was divided into four periods (60 to 84, 85 to 108, 109 to 132, and more than 132 months). Duration of treatment with ARV was measured in months, and all patients had been treated for at least 60 months. The use of ARV with PI, the irregular use of ARV and the use of PI for more than six months were qualitative variables, and the information was obtained from medical records and on the pharmacy report. The current ARV class used for treatment was divided into four groups: 2NRTI + 1NNRTI; 2NRTI + 1PI; NRTI + NNRTI + PI, among others. The type of current scheme can also be subdivided into schemes with PI with ritonavir (PI/r), others with PI without ritonavir (PI w/r) and other without PI.

The highest and most current VL were considered, being quantitatively analyzed and divided into four groups: undetectable (lower than 50 copies/mL); low (lower than 10,000 copies/mL); moderate (from 10,000 and 100,000 copies/mL) and high (>100,000 copies/mL).

As to CD4 (lymphocyte count), we considered the lowest count throughout the life of the patient and the current count, which was quantitatively analyzed and classified into risk categories: low risk (more than 500 cells/mm^3); moderate risk(from 200 to 500 cells/mm^3); and severe risk (less than 200 cells/mm^3).

Statistical analysis

The qualitative variables were shown by the distribution of frequencies, and the quantitative ones were analyzed as means, medians, standard deviation, minimum and maximum.

Pearson's correlation coefficient was used in order to compare IMC values in the RCC automatic mean with the quantitative variables. Student's *t* test and the analysis of variance (ANOVA) were used for qualitative analysis.

The defined significance level was 5%. Statistics was performed with the SPSS software for Windows, version 12.0 – Statistical Package for the Social Science.

Sample characteristics

The sample was comprised of 70 individuals with AIDS. Table 1 presents the sample profile for biological and socioeconomic variables. The population consisted mostly of males (60%), and mean age was 40.5 years; all of them had been diagnosed and treated with ARV for at least five years. Mean time from HIV diagnosis was 104.9 months (ranging from 60 to 228), being 25 (35.7%) with 60 to 84 months and 9 (12.9%) with more than 132 months. Mean duration of HIV treatment was 97.9 months (ranging from 60 to 180 months). Concerning the type of treatment, 49 (70.0%) used or were currently using ARV with the PI class; 47 patients (67.1%) used it for more than six months, and 36 (51.4%) were currently using PI.

The individuals in the study were questioned and evaluated as to classic risk factors for atherosclerosis: SAH, smoking, obesity, hypercholesterolemia, hypertriglyceridemia and family history of cardiovascular events: AMI, angina, stroke or POAD (Table 1). In the evaluation of cardiovascular history, 29 (41.4%) had family history.

Results

ABI was increased in both lower limbs in one patient (0.7%). Mean ABI was 1.082 (SD=0.089) in the right lower limb (RLL) and 1.080 (SD=0.082) in the left lower limb (LLL)

The IMC was not thickened in any analyzed patient, with mean of 0.51 mm (SD=0.08) on the RCC and 0.52 mm (SD=0.09) on the LCC.

Table 2 presents the distribution of frequencies of the clinical characteristics of the group of 70 patients infected by the HIV.

Table 3 described specific variables related to HIV. The mean value of the recent VL was 7,889.09. It was calculated for only 11 patients, since all other patients had undetectable current VL values. Sixty three patients had mean higher VL of 153,698.00; the remaining seven patients always had undetectable VL.

Table 1. Sample profile of the studied population for the socioeconomic variables and risk factors for atherosclerosis.

Variables	n	%
Age (years)		
Mean±SD	40.5±6.0	
Minimum – Maximum	24–50	
Gender		
Male	42	60.0
Female	28	40.0
Schooling		
Illiterate and <8 years	31	44.3
Literate >8 years	39	55.7
Income (Reais)		
Mean±SD	511.8±224.3	
Minimum – Maximum	200–1,800	
Ethnicity		
White	33	47.1
Black	16	22.9
Brown	21	30.0
Smoking	12	17.1
SAH	11	15.7
High cholesterol	25	35.7
High triglyceride	32	45.7
High BMI	25	35.7
Altered AC	10	14.3

Base: 70 patients; SD – standard deviation; AC – abdominal circumference.

Table 2. Distribution of the frequency of qualitative variables related to the infection by the HIV and its treatment.

Variables	n	%
Time of HIV		
60 to 84 months	25	35.7
85 to 108 months	16	22.9
109 to 132 months	20	28.6
>132 months	9	12.9
Use of ARV with PI		
No	21	30.0
Yes	49	70.0
Irregular use of ARV		
No	66	94.3
Yes	4	5.7
PI for more than 6 months		
No	23	32.9
Yes	47	67.1
Current class		
2NRTI + 1NNRTI	34	48.6
2NRTI + 1PI	25	35.7
NRTI + NNRTI + PI	6	8.6
Others	5	7.1
Type of scheme		
With PI/r	29	41.4
With PI w/r	7	10.0
Without PI	34	48.6
Current VL		
Undetectable <50 copies/mL	60	85.7
Low <10,000 copies/mL	7	10.0
Moderate= 10,000 – 100,000	3	4.3
High >100,000 copies/mL	0	0.0
Higher VL		
Undetectable <50 copies/mL	7	10.0
Low <10,000 copies/mL	15	21.4
Moderate 10,000 – 100,000	22	31.4
High >100,000 copies/mL	26	37.1

Base: 70 patients with HIV.

In Table 4, we see there is no statistically significant correlation of the IMC measurement in RCC (automatic mean) with any of the analyzed variables, that is, none of these variables interfered in the value of IMC in this study.

It is possible to notice that, in Tables 5 to 7, the type of adopted scheme and the VL do not interfere in the IMC. Considering there is statistical trend with p<0.10, in Table 6 the mean automatic comparison of IMC in RCC with the current class of ARV, the IMC was thicker in the NRTI+NNRTI+PI (0.56 cm) and in the "others" class (0.56 mm), and the general mean was 0.51 mm (p=0.081). Both classes had the lower number of patients, and possibly, if the sample had been larger, this statistical trend might have been more expressive. Considering this same trend in Table 7, comparing the automatic mean of IMC in the RCC with the current VL, IMC was not as thick in groups with low VL (0.46 mm), and moderate (0.44 mm), with p=0.077. These groups also had a smaller population in relation to the group with undetectable VL, and, in a larger sample, this statistical trend could be more expressive.

Only two patients had atheromatous plaque on the RCC, and none on the LCC. There was no statistically significant difference in relation to the presence of the plaque and the use of PI *versus* the absence of PI, not even when variables related to HIV were considered.

Discussion

In this study, the automatic measurement in the right and left common carotid arteries did not show thickening of the of IMC. ABI was increased in only one patient (0.7%) with incompressible arteries.

Some authors have suggested that the association of ARVT with dyslipidemia and insulin resistance is common, and it persists particularly in patients treated with PI. The pathogenesis of this metabolic abnormality is not completely understood, but it involves direct effects of the PI, lipodystrophy and factors not related to the treatment[22]. In this study, 25 (35.7%) patients presented with hypercholesterolemia and 32 (45.7%) had hypertriglyceridemia. As to the use of PI in the treatment, 47 (67.1%) used it for more than six months, and 36 (51.4%) were currently using it, but no IMC thickening was identified. The hypothesis that the PI causes early thickening of the complex is not confirmed in this study, even in the presence of dyslipidemia. A possible reason for not finding IMC thickening and changes in the ABI in this population is that the participants were young (mean of 40.5 years) and had fewer risk factors for atherosclerosis than in other studies.

Some investigators defend the hypothesis that ARVT induces the activation of the endothelial function. Thus, both the HIV and the immune response of the reconstitution organism and PART can promote the early endothelial activation[41-43]. Since no IMC thickening was registered in this study, it was demonstrated that there is no association between the thickening of the complex with time of treatment, type of treatment or the presence of HIV. The patients had been diagnosed with AIDS and had been medically treated for at least five years. It is worth to mention that this

Table 3. Descriptive statistics of the quantitative variables related to the infection by the HIV and its treatment.

Variables	n	Mean	Median	Standard Deviation	Minimum	Maximum
Time of HIV (months)	70	104.91	102.00	±34.11	60	228
Time of treatment (years)	70	8.16	8.00	±2.62	5	15
Number of schemes	70	2,47	2,00	±1,35	1	6
Recent CD4	70	670.57	627.50	±321.35	88	1675
Smaller CD4	70	175.07	151.50	±123.80	5	642
Recent VL value	11	7,889.09	4,135.00	±11,256.63	129	40,000
Higher VL	63	153,692.00	804,00.00	±195,888.37	640	750,000

Base: 70 patients with HIV; VL – viral load.

Table 4. Coefficient correlation of the variables related to the infection by the HIV and its treatment with the measurement of IMC and RCC (automatic mean).

Variables	Correlation	p-value
Time of HIV (months)	0.047	0.700
Time of treatment (months)	0.030	0.803
Number of schemes	0.019	0.879
Current CD4	0.093	0.446
Smaller CD4	-0.087	0.472
Recent VL	0.072	0.833
Higher VL	0.082	0.522

ANOVA; VL – viral load.

population has been treated for a long time (mean of 97.9 months), and that 59 (84.0%) had current undetectable VL with mean of current CD4 of 670.6, which shows that these patients were mostly clinically stable. So, the endothelium is less activated, and this is a possible reason for the IMC not to be thickened.

The lack of a significant association between the IMC thickening in patients with HIV using PI, when compared to control patients who are not on PI or to people who do not have HIV, has been identified in other observational studies of some cohorts[29,30,43]. Currier et al. suggest that the thickened IMC identified by ultrasound is a consequence of traditional risk factors for

Table 5. Comparison of the IMC in RCC (automatic mean) with the type of scheme (with and without PI).

Type of scheme	n	Mean	Median	Standard deviation	Minimum	Maximum
HIV with PI	36	0.51	0.51	0.07	0.35	0.67
HIV without PI	34	0.51	0.49	0.09	0.36	0.78
Total	70	0.51	0.50	0.08	0.35	0.78

p=0.890.

Table 6. Comparison of the IMC in RCC (automatic mean) with the type of the used antiretroviral scheme.

Current class	n	Media	Median	Standard deviation	Minimum	Maximum
2NRTI +1NNRTI	34	0.51	0.49	0.09	0.36	0.78
2NRTI + 1PI	25	0.49	0.49	0.05	0.35	0.58
NRTI + NNRTI +PI	6	0.56	0.60	0.09	0.46	0.67
Others	5	0.56	0.54	0.08	0.46	0.65
Total	70	0.51	0.50	0.08	0.35	0.78

p=0.081.

Table 7. Comparison of the IMC in RCC (automatic mean) with the viral load (VL).

Current viral load	n	Mean	Median	Standard deviation	Minimum	Maximum
Undetectable	60	0.52	0.51	0.08	0.36	0.78
Low	7	0.46	0.46	0.07	0.35	0.55
Moderate	3	0.44	0.46	0.06	0.38	0.49
Total	70	0.51	0.50	0.08	0.35	0.78

p=0.077.

atherosclerosis, and it is more important than the impact of PI to thicken the complex[29]. Authors who studied a prospective and multicentric cohort with 423 patients with HIV, whose IMC was analyzed by an ultrasound, concluded that only classic cardiovascular risk factors had an independent association with the increased IMC in patients infected by the HIV. In the multivariate analysis, the effect of lipodystrophy and ARVT disappeared after adjustment for other cardiovascular risk factors[43]. In this study, lipodystrophy, age, gender, BMI, smoking, alcohol consumption, SAH, AIDS stage, type and duration of PART, CD4, insulin, total cholesterol and homocysteine were taking into account. Mean IMC in the carotid arteries of this cohort was 0.54 mm (ranging from 0.50 to 0.60). In the population of the present study, mean IMC was 0.51 mm in the RCC, and 0.53 mm in the LCC. These measurements were similar to those of other researchers when analyzing similar risk factors[43]. In other study, authors evaluated the IMC of 346 patients infected by the HIV and followed-up for 12 months, and the conclusion was also that classic cardiovascular risk factors are the most determinant in the progression of IMC thickness. The connection between the immunologic status and the IMC of the carotid arteries requires new studies[30].

Some authors concluded that the predictive factors for low ABI were: age, smoking, diabetes and CD4 lower than 200 cells/μL[44]. Other investigators could not find a significant association with low ABI[45,46]. In the univariate analysis, Gutiérrez et al. observed there was a significant difference for low ABI when there were four classic cardiovascular risk factors *versus* two (p=0.015) and low CD4 count[47]. In the multivariate analysis of Ollala et al.[15], PI, dyslipidemia and low CD4 were related to an abnormal ABI. The authors of this metanalysis concluded that the prevalence of abnormal ABI was higher in patients infected with HIV, and also that the use of PI may be related to this finding; also, that the use of ABI can be a way to identify patients with high cardiovascular risk[15]. In the current sample, the only patient with altered ABI used PI. A larger sample with cases of altered ABI would be necessary to test the association of the increased ABI with the use of PI.

Conclusion

The findings lead to the conclusion that young individuals who used ARVT for five years or more did not present IMC thickening or changes in the ABI. There was no difference in the IMC thickening associated with the type of ARV scheme used or the VL level, except for a trend in the schemes with NNRTI and PI.

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