Atherosclerosis 246 (2016) 301–308

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Randomized trial of a multidisciplinary lifestyle intervention in HIV-infected patients with moderate-high cardiovascular risk

Maria Saumoy [a, *], Carlos Alonso-Villaverde [b], Antonio Navarro [a], Montserrat Olmo [a], Ramon Vila [c], Josep Maria Ramon [d], Silvana Di Yacovo [a], Elena Ferrer [a], Jordi Curto [a], Antonio Vernet [e], Antonia Vila [a], Daniel Podzamczer [a]

[a] HIV Unit, Infectious Disease Service, Bellvitge University Hospital, Bellvitge Biomedical Research Institute, Hospitalet de Llobregat, Spain
[b] Unitat Clínica CS Llevant, Hospital Santa Tecla, Tarragona, Spain
[c] Vascular Surgery Service, Bellvitge University Hospital, Hospitalet de Llobregat, Spain
[d] Preventive Medicine Service, Bellvitge University Hospital, Hospitalet de Llobregat, Spain
[e] Department of Mechanical Engineering, Universitat Rovira i Virgili, Tarragona, Spain

ARTICLE INFO

Article history:
Received 8 July 2015
Received in revised form
29 December 2015
Accepted 9 January 2016
Available online 11 January 2016

Keywords:
Lifestyle intervention
Cardiovascular risk
Carotid intima-media thickness
Carotid plaques
Biomarkers

ABSTRACT

Objective: To assess the impact of a multidisciplinary lifestyle intervention on cardiovascular risk and carotid intima-media thickness (c-IMT) in HIV-infected patients with Framingham scores (FS) > 10%.
Design: Randomized pilot study; follow-up 36 months.
Methods: Virologically suppressed adult HIV-1-infected patients with FS >10% were randomized 1:1 to the intervention group (multidisciplinary lifestyle intervention) or control group (routine care). At baseline and months 12, 24 and 36, lipid parameters were analyzed and carotid ultrasound was performed to determine c-IMT and presence of plaques. Biomarkers were measured at baseline and month 36. The primary endpoints were lipid and FS changes at 36 months.
Results: Fifty-four patients were included, 27 in each arm. Median age was 50.5 years, all patients but one were men, and FS was 16.5%. Relative to controls, total and LDL cholesterol had significantly decreased in the intervention group at 24 months ($p = 0.039$, $p = 0.011$, respectively). However, no differences between groups were found at month 36 in lipid variables, neither in FS. Tobacco use decreased in the intervention group ($p = 0.031$). At baseline, 74.5% of patients had subclinical atherosclerosis, and at month 36, we observed a progression in c-IMT that was greater in the intervention group ($p = 0.030$). D-dimer increased ($p = 0.027$) and soluble intercellular adhesion molecule-1 decreased ($p = 0.018$) at 36 months.
Conclusions: In this cohort of HIV-infected patients with FS>10% and a high percentage of subclinical atherosclerosis, a multidisciplinary lifestyle intervention resulted in a slight improvement in some cardiovascular risk factors and the FS during the first 2 years, but did not prevent c-IMT progression.

1. Introduction

HIV-infected patients are at a higher risk of developing cardiovascular disease than the general population [1,2]. HIV infection itself, combined antiretroviral therapy (c-ART), and traditional cardiovascular risk factors interact in the pathogenesis of atherosclerosis [3]. HIV is associated with persistent inflammation and immune activation. As compared to healthy controls, several biomarkers related to the pathogenesis of atherosclerosis are elevated in treatment-naïve HIV-infected patients. Initiation of c-ART leads to a decrease in some of these markers, whereas others remain elevated or higher than in controls [4–6]. In addition, c-ART, mainly protease inhibitors and some nucleoside reverse transcriptase inhibitors, are associated with disturbances in lipid metabolism (elevated total cholesterol, low-density lipoprotein cholesterol, and triglycerides) and glucose metabolism (insulin resistance, glucose intolerance, and diabetes) [7]. Finally, traditional cardiovascular risk factors such as dyslipidemia, hypertension, and diabetes are more common and present at a younger age in HIV-infected

* Corresponding author. HIV Unit, Infectious Disease Service, Hospital Universitari de Bellvitge, C/Feixa Llarga s/n, 08907 Hospitalet de Llobregat, Spain.
E-mail address: msaumoy@bellvitgehospital.cat (M. Saumoy).

http://dx.doi.org/10.1016/j.atherosclerosis.2016.01.014
0021-9150/

patients than in the general population [1].

Lifestyle interventions are the first step in cardiovascular risk management [8], but information is limited regarding the impact of these interventions on metabolic disorders [9–11] and subclinical atherosclerosis [12] in HIV-infected patients.

We conducted a pilot study in which patients with estimated cardiovascular risk greater than 10% determined by the Framingham Score (FS) were randomized to a multidisciplinary lifestyle intervention (intervention group) versus routine care (control group) with the aim of assessing the impact of the intervention on the patients' cardiovascular risk status, lipid profile, carotid intima-media thickness (c-IMT), and cardiovascular biomarkers over a 36-month follow-up.

2. Methods

2.1. Study design, patient population, and endpoints

This is a randomized, controlled pilot trial carried out in the HIV unit of a university teaching hospital. The inclusion criteria were documented HIV infection, age older than 18 years, stable antiretroviral regimen, undetectable viral load for the previous 3 months, and estimated cardiovascular risk greater than 10% based on the FS. The exclusion criteria were previous cardiovascular disease, diabetes mellitus, microalbuminuria, dyslipidemia due to hypothyroidism, nephrotic syndrome or renal insufficiency (estimated glomerular filtration measured by the Cockcroft-Gault equation <50 mL/min), or decompensated cirrhosis.

The study (registration number ISRCTN11313360) was approved by the hospital ethics committee and written consent for participation was signed by all patients.

Patients were randomized 1:1 into 2 groups by stratified random allocation according to sex, age, and cardiovascular risk. In the intervention group, patients underwent an intensive, multidisciplinary lifestyle intervention, imparted by a dietitian and a preventive health physician. In the control group, patients continued with routine care and received lifestyle recommendations.

The primary endpoints were changes in lipid parameters and FS at 36 months in the 2 groups. The secondary endpoints were changes in c-IMT and cardiovascular biomarker at 36 months in the two groups.

2.2. Clinical intervention

In the intervention group, patients underwent an intensive lifestyle intervention that included a dietary program, exercise recommendations, and a plan to quit smoking. In the dietary program, patients were visited at baseline, at months 1–6, 8, 10, and 12, and every 4 months thereafter. At baseline, the dietitian imparted an educational intervention informing of the need to adopt a cardio-healthy diet, which involved a reduction in saturated fatty acids and refined sugar intake and an increase in polyunsaturated and monounsaturated fatty acids and fiber. The diet emphasized the benefits of eating cold-water fish, olive oil, whole grains, vegetables, and fruits and decreasing consumption of red meat and products containing white sugar. In addition, the dietitian provided several documents related to balanced diets, and designed an individualized meal plan for each patient. During the time between visits, patients recorded their daily food intake for 3 non-consecutive days. At each visit, the dietician performed a 24-h dietary recall to assess the patient's intake, modify incorrect eating habits, and strengthen cardio-healthy habits. In addition, patients were advised to practice moderate aerobic exercise 3 days a week.

In the plan to quit smoking, patients first underwent baseline evaluation to determine current tobacco use, psychosocial characteristics (Beck Depression Inventory and Hamilton Anxiety Rating scales), and the intensity of addiction to nicotine (Fagerstrom Test for Nicotine Dependence). Participants were seen by a preventive health physician at weeks 1, 2, 3, 5, 8, 10, 12, and 24. At each visit, smokers attended a previously standardized behavioral counseling session that lasted 15 min and was based on motivational interviewing. The sessions included practical counseling elements, such as problem solving and skills training. All smokers received nicotine replacement therapy or bupropion at standard doses. At each clinical visit, the physician recorded compliance with therapy, adverse events, and number of cigarettes smoked, and patients underwent exhaled carbon monoxide testing.

In the control group, patients were seen every 4 months. The investigator provided documents containing recommendations about a balanced diet and regular physical activity and reminders about the desirability of stopping smoking; patients were referred to the preventive medicine physician if they requested a visit.

Cardiovascular risk factors were evaluated and managed every 4 months in both groups, following the NCEP Adult Treatment Panel III guidelines [8]. The target value in the guidelines for low-density lipoprotein cholesterol (LDL-c) is $\leq$ 3.37 mmol/L. If plasma LDL-c was $\geq$3.37 mmol/L after 4 months of diet counseling, a statin was started, and if levels persisted above this value, statin dose was increased or ezetemibe was added to the patient's regimen. Blood pressure was assessed at each visit, with targets of $\leq$140 mmHg for systolic and $\leq$90 mmHg for diastolic blood pressure. When blood pressure values exceeded the target value at 3 evaluations after dietary counseling, an antihypertensive drug was prescribed. Diabetes was diagnosed when fasting plasma glucose level was $\geq$7 mmol/L. If elevated levels persisted after 4 months, an antidiabetic drug was prescribed. If glucose control was not achieved (HBA1c >6.5%), the patient was referred to a general practitioner or endocrinologist. Tobacco use was recorded at each visit.

2.3. Laboratory assessment

Venous blood samples were obtained after an overnight fast every 4 months. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c) and triglycerides (TG) were measured using an enzymatic colorimetric method. LDL-c was calculated using the Friedewald equation (LDLc = TC − HDLc − (TG/2.17)).

At baseline, and months 12, 24, and 36, insulin was measured by an immunochemiluminescent assay (Immulite 2000, Siemens Health Care Diagnostics). At baseline and month 36, a blood sample was centrifuged and plasma was refrigerated at −70 °C for subsequent analysis. The following biomarkers were measured on a Luminex 200 xMAP system (Millipore Corporation, Billerica, MA, USA): inflammatory biomarkers (interleukin-6 [IL-6], tumor necrosis factor-alfa [TNF-α], high-sensitivity C-reactive protein [hs-CRP], fibrinogen), endothelial biomarkers (monocyte chemoattractant protein-1 [MCP-1], soluble intercellular adhesion molecule-1 [sICAM-1], L-selectin, and fractalkine), coagulation biomarkers (sCD40, D-dimer, and plasminogen activator inhibitor-1 [PAI-1]) and adiponectin. Asymmetric dimethylarginine (ADMA) was measured using a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) (Central Plains Road, Yangpu District, Shanghai, China). Soluble CD163 was measured by ELISA (Boston Biochem, 840 Memorial Drive, Cambridge, MA, USA).

The estimated overall cardiovascular risk over the next 10 years was calculated using the FS [13].