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Brief Report

Short-term folinic acid supplementation and aerobic exercise improve vascular reactivity in HIV-infected individuals

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Abstract

The aim of this study was to determine the effect of supervised exercise and folinic acid supplementation on endothelial function in HIV-infected individuals. A randomized clinical trial, double blinded, was conducted with 16 HIV-infected individuals, antiretroviral therapy (at least 6 months) with undetectable viral load (<50 copies/mL), and CD4 count > 200 cells/mm^3. The subjects were randomized to aerobic exercise (n = 5) and daily intake for 4 weeks of 5 mg of folinic acid (n = 6) or placebo (n = 5) groups. To assess endothelial function, venous occlusion plethysmography in the brachial artery by the protocol of reactive hyperemia was performed. The aerobic

Exercise group (Δ6.5 mL/min/100 mL) and folinic acid group (Δ7.3 mL/min/100 mL) improved reactive hyperemia, but no difference was found in placebo group (from Δ −0.3 ml/min/100 ml, time $p < 0.001$, interaction $p = 0.02$). Results demonstrate that supervised exercise and folinic acid supplementation in very short term improve endothelial function in HIV-infected individuals. As exercise and folate supplementation are safe and relatively inexpensive, this finding deserves more attention in large randomized clinical trials in an attempt to reduce cardiovascular risk in HIV-infected population.

Keywords:

Exercise training | Endothelial function | HIV

Introduction

The antiretroviral therapy (ART) has dramatically reduced the morbidity and mortality associated to HIV.[1] On the other hand, with longer life expectancy, metabolic chronic non-communicable diseases are more prevalent in patients under ART therapy when compared to naïve patients.[2,3] In this scenario, cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality in such population,[4–6] and the possible mechanisms of raised incidence could be related to endothelial dysfunction.[7–12] Therefore, we believe that it should be important to identify and manage individuals with endothelial dysfunction early on, which compromises up to 35% of these patients.[13,14]

Our previous report has shown that supplementation with folates improves endothelium-dependent vasodilatation in HIV patients.[15] However, non-farmocologic safe strategies[16] have been considered to reduce cardiovascular complications, such as exercise as an additional therapy, since the ARV treatment involves increased cardiovascular risks. Previously, acute responses to exercise demonstrated potential benefits.[17] Also, chronic effects (exercise training) have been used to improve endothelial function in patients such as obese[18,19] and peripheral arterial disease patients[20] (Table 1).

Nevertheless, there is still no study evaluating the effect of folinic acid supplementation when compared to exercise intervention on endothelial function in HIV patients. This study aimed to determine whether 4-weeks of folinic acid supplementation (5 mg/day) and aerobic exercise training would improve vascular reactivity, as assessed by brachial artery reactive hyperemia in HIV-infected people. For that, we conducted a pilot randomized, double-blind, placebo-controlled trial, with HIV-infected individuals, aged 18y or over, on ART for at least 6 months, with undetectable viral load (less than 50 copies/ml), and CD4 counts more than 200 cells/mm^3. Exclusion criteria were diabetes mellitus, active infection, liver, kidney or cardiovascular diseases, pregnancy, and illicit drug use. All regular medications were maintained. The protocol was approved by the committee for ethics in research of the Hospital de Clínicas de Porto Alegre, according to Declaration of Helsinki, and all participants gave written informed consent.

Population and methods

Participants were randomly assigned to a 4-week treatment with either folinic acid (n = 6) or placebo (n = 5) both blinded to the researcher and participants as described before,[15] and a not blinded arm of exercise group (n = 5). The primary outcome measure was the assessment of brachial artery vascular responses during reactive hyperemia. Secondary outcomes were the changes on the biochemical and hemodynamic variables. All outcomes were blinded for the evaluators and statistician.

In short, reactive hyperemia (RH) was induced by placing a cuff in the upper-arm at 250 mm Hg, and releasing after 5 min, in dominant forearm. All flow recordings were manually traced by an operator who was blinded to the groups, and time. After 15 min of rest, 2.5 mg of sublingual isossorbide dinitrate (Isordil®/Sigma/Brazil) was administered as an endothelium-independent vasodilator. Five minutes later, endothelium-independent vasodilatation of the brachial artery was measured.[21] Folinic acid and placebo capsules were indistinguishable in shape, size, as well as color. They were pre-packed in identical bottles and consecutively numbered for each patient,

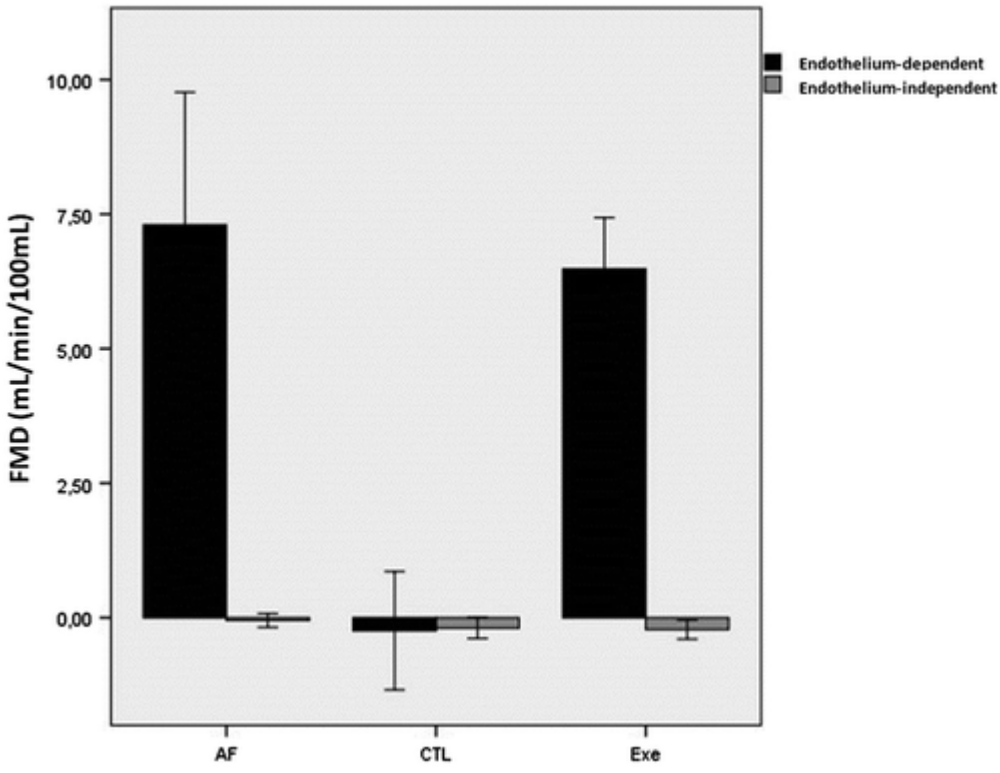
investigators nor the participants were aware of the contents. Reported compliance was 100% of prescription in all groups. Missed supervised exercise sessions were replaced in the same week.

Results

Our results showed no significant change in hemodynamic and biochemical variables. Likewise, blood glucose, lipid profile, creatinine, and vitamin B_{12} did not change significantly in the three groups after intervention (data not showed).

Figure 1 shows the delta of reactive hyperemia response and endothelium-dependent vasodilation responses (blue bars) after the 4 weeks. Exercise improves reactive hyperemia (9.4–15.9 mL/min/100 mL) and folinic acid (11.9–19.2 mL/min/100 mL). The same was not observed in the placebo group (from 18.7 to 18.4 ml/min/100 ml, time $p < 0.001$, interaction $p = 0.02$). The endothelium-independent responses (green bars) remained unchanged in both groups (groups $p = 0.67$; interaction $p = 0.73$). No adverse effects were observed.

Figure 1 Deltas and SE of reactive hyperemia (FMD), endothelium-dependent and independent, after 4-weeks intervention in HIV patients.



The main finding of this small randomized clinical trial was that short-term interventions of oral folinic acid supplementation and aerobic exercise improved similarly endothelial-dependent vasodilation in HIV-infected people. To the best of our knowledge, this is the first study to investigate the effect of short-term intervention of aerobic exercise when compared to folinic acid supplementation on endothelial function in this population. Our results extend these vascular benefits to HIV-infected people on stable antiretroviral therapy. More importantly, both interventions are low cost and could be easily implemented in the clinical site routine. However, non-supervised exercise effect (counseling and home-based strategies) still needs to be tested in these patients.

In conclusion, our preliminary results demonstrate that short-term administration methylated folate derivative from folinic acid, and aerobic exercise training improve endothelium-dependent vasodilatation in HIV-infected individuals. This finding deserves more attention in larger randomized clinical trials, and future studies should also evaluate whether prolonged interventions would be effective to improve cardiovascular risks and major cardiovascular events in these population.

Contributors

SSG, ES, JPR, PABR conceived and designed the experiments. SSG was responsible for data collection. SSG, PABR analyzed data. SSG, PABR wrote the paper. The Final review was done by ES, PABR.

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