Effect of exercise and strength training on cardiovascular status in HIV-infected patients receiving highly active antiretroviral therapy

Daniele Scevola[a], Angela Di Matteo[a], Paolo Lanzarini[a], Filippo Uberti[a], Silvia Scevola[b], Verginia Bernini[a], Greta Spoladore[a] and Angela Faga[b]

A routine evaluation of lipid metabolism and body fat distribution along with a careful cardiovascular risk stratification according to international guidelines are required for HIV-infected patients receiving highly active antiretroviral therapy. Intervention includes evaluation of patients for both epidemiological and clinical factors, and for anthropometric and biochemical parameters. Diet counseling, prescription of antihyperlipidemic drugs and exercise training are the cornerstones of programs devoted to protecting patients from side effects of therapies that compromise quality of life and the functions of organs like the pancreas and heart that are involved in lipid disorders.

AIDS 2003, **17** (suppl 1):S123–S129

Keywords: exercise, heart disease, lipodystrophy, HIV, highly active antiretroviral therapy

Introduction

Since 1996, the year in which highly active antiretroviral therapy (HAART) was introduced, the number of patients who have died from AIDS and opportunistic infections has decreased by two-thirds [1]. However, new disorders regarding lipids, glucose metabolism and body fat have gained more clinical importance [2,3]. A significant portion, ranging from 5 to 75%, of HIV-infected patients receiving HAART have changes in lipid metabolism and body fat distribution after an average time of 10–12 months on therapy [3]. The improved survival of HIV patients receiving HAART has been associated with elevated triglycerides, low-density lipoprotein (LDL) cholesterol, very low density lipoprotein (VLDL) cholesterol and decreased high-density lipoprotein (HDL) cholesterol. It has also been associated with fat distribution abnormalities (peripheral lipoatrophy and visceral fat accumulation), and with cardiovascular abnormalities [3–14] (Table 1). These metabolic and anatomic alterations may increase cardiovascular morbidity, compromising quality of life and the otherwise favorable results of HAART. New therapeutic strategies addressed to prevent and manage emerging metabolic and fat distribution abnormalities have become critically important [15,16].

Coronary heart disease (CHD) is the leading cause of death and a common cause of morbidity in Western countries. Approximately 14 million Americans, according to NHANES III data, have CHD [17]. Annually, about 1.1 million people experience a myocardial infarction, and about 500 000 die from CHD. Deaths due to CHD in the United States are currently close to the Healthy People 2000 target that was set by the Department of Health and Human Services at 104 per 100 000, declining from 135 per 100 000 in 1985 to 108 per 100 000 in 1995. The objective proposed for the year 2010 is to reduce CHD deaths to no more than 51 per 100 000, 'enhancing the cardiovascular health and quality of life of all Americans through improvement of medical management, prevention and control risk factors, and promotion of healthy lifestyle behaviors' [18]. In light of this policy,

From the [a]Department of Infectious Diseases, IRCCS Policlinico S. Matteo and [b]IRCCS Fondazione S Maugeri, Plastic Surgery Section, University of Pavia, Italy.

Requests for reprints to Prof. Daniele Scevola, M.D., Department of Infectious Diseases, University of Pavia, IRCCS Policlinico S. Matteo, 27100 Pavia, Italy. Tel: +39 382 502 672; Fax: +39 382 423 320; e-mail: scevdan@unipv.it

Table 1. Differences between wasting and lipodystrophy.

	Wasting	Lipodystrophy
Body weight	⇓	⇑ or ⇓
Body fat	⇓ All areas	Peripheral ⇓ Central ⇑
Lean body mass	⇓	Unchanged
Total cholesterol	⇓	⇑
Very low-density lipoprotein cholesterol	⇓	⇑
Low-density lipoprotein cholesterol	⇓	⇑
High-density lipoprotein cholesterol	⇓	⇓
Triglycerides	⇑	⇑⇑
Diabetes/insulin resistance	No	Yes
Coronary heart disease	No	Yes

which was also adopted by the European Community, particular attention must be devoted to HIV-infected people, a group that could represent an emerging population at more elevated risk of CHD due to the prolonged expectancy of life and/or metabolic disturbances induced by therapy.

Many patients meet the intervention criteria defined by the American National Cholesterol Education Program [19], including evaluation methods, diet, drug and exercise treatment.

Evaluation criteria

Patients at risk of development of CHD must be routinely evaluated for family history of CHD, smoking, hypertension, hormonal status, obesity, physical activity, alcohol abuse, hypogonadism, hypothyroidism, diabetes, and renal or hepatic disease.

Measurement of total cholesterol, HDL cholesterol, LDL cholesterol and very low density lipoprotein cholesterol, triglycerides, and lactate should be performed [20,21]. The body composition and body energy content evaluation are an essential part of our investigation protocol [22]. The resting metabolic rate (RMR) is the measurement of the energy expended for maintenance of normal body functions and homeostasis, and it represents the largest portion of daily energy expenditure (60–75%) [23–25]. The importance of this parameter derives from the fact that the RMR includes resting cardiovascular and pulmonary functions. World Health Organization formulae that consider body weight and height [26] or bioimpedance analysis can be used to predict the RMR for different age and sex groups, but the most useful method for measuring the energy expenditure is indirect calorimetry [27,28]. Energy production is estimated by measuring O_2 consumption and CO_2 production by special calorimeter (e.g. Datex-Engstron Division Instrumentarium Corp. Helsinki, Finland. Type MBM-200-23-01). Typical RMR values range from 0.7 to 1.6 kcal/min depending on the subject's body composition, gender, and/or level of training.

Intervention criteria

Diet

No accepted guidelines exist for the treatment of lipodystrophy syndrome and related disorders in HIV-infected patients. However, according to the American National Cholesterol Education Program (Adult Treatment Panel III) [19,29], among patients with pre-existing CHD, dietary intervention is indicated when the LDL cholesterol level ranges between 100 and 130 mg/dl, and drug therapy is recommended if LDL cholesterol is $>$ 130 mg/dl. Among patients without CHD but with two or more risk factors, dietary intervention is indicated when the LDL cholesterol level is between 130 and 160 mg/dl. Drug therapy must be added when LDL cholesterol $>$ 160 mg/dl. In patients with fewer than two risk factors, dietary modifications should be initiated when LDL cholesterol levels range between 160 and 190 mg/dl. In these lower risk patients, drug therapy should be considered with LDL cholesterol $>$ 190 mg/dl. In patients with very high triglyceride levels ($>$ 400 mg/dl), the Adult AIDS Clinical Trials Group [30] suggests a dietary intervention when total cholesterol is $>$ 240 mg/dl or HDL cholesterol $<$ 35 mg/dl. In isolated hypertriglyceridemia, patients with fasting serum levels $>$ 200 mg/dl should follow diet and exercise. If levels are higher than 1000 mg/dl, drug therapy should be strongly suggested because of the risk of pancreatitis. The same indication should be considered for patients with a history of pancreatitis with triglycerides $>$ 500 mg/dl.

Prior to considering drug therapy, it is recommended to try dietary and exercise interventions to reduce hypercholesterolemia. In patients with competing dietary needs for wasting and lipids alterations, it is preferable to address the wasting first [28,31].

Guidelines for dietary interventions must consider each patient's RMR, gut functions, concomitant diseases,

hormonal status, appetite, and social conditions, as previously described [22,30,32]. When signs of malnutrition appear in a patient (weight loss, fat loss, lipoatrophy, lipodystrophy, muscular atrophy, skinfold thinning), suitable nutritional treatment is advised [28].

Adequate nutritional status has a positive effect on the basic illness and on the quality of life. In the case of malnutrition, lipids must be prescribed to avoid an essential fatty acid deficit. A reduced supply of n-6 polyunsaturated fatty acids and an increased supply of n-3 polyunsaturated fatty acids may modulate the phlogistic process and cytokine production. This effect seems to be due to eicosapentaenoic acid. This acid together with docosahexaenoic acid are the main component of fish oil. In contrast to other fatty acids of the n-3 and n-6 series, eicosapentaenoic acid is a direct suppressant of lipid mobilization factor in '*in vitro*' and '*in vivo*' studies, and counteracts weight loss, lipolysis and protein catabolism [33]. To block protein loss, it is necessary to administer 1.5–2.0 g/kg amino acids per day, of which < 0.7 g/kg should be essential amino acids. Selective mixtures of branched-chain amino acids are useful in patients with liver disease, especially those with encephalopathy. An early and aggressive nutritional treatment may improve the prognosis and reduce the duration of hospital stay.

Unfortunately, nutritional therapy programs with the addition of nourishment and oral integrators may not be fully funded by many private and public health providers.

Appetite-stimulating drugs, such as cyproheptadine [34], medroxyprogesterone acetate [35,36], megestrol acetate [31,37], insulin-like growth factor-1 [38], corticosteroid and growth hormone [39,40], may contribute to the success of any nutritional program.

Drugs

Because an adequate diet and the adoption of a physical exercise program helps to reduce lipid levels in only 40% of patients [19], drug therapy with statins and/or fibrates for hypercholesterolemia and/or hypertriglyceridemia may become necessary [30]. In the first group (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors), 10–40 mg pravastatin orally every day or 10–40 mg atorvastatin orally every day are preferred because they are the least susceptible to potentially dangerous interactions with protease inhibitors. An alternative is 20–80 mg fluvastatin orally twice daily. Lovastatin (20–80 mg orally twice daily) or 20–80 mg simvastatin orally once daily with evening meal may have increased risk of myopathy when used with fibrates, and simvastatin levels may be increased substantially. In the second group (fibrates), 1 g clofibrate orally twice daily or 600 mg gemfibrozil orally twice daily before meals, or 54–160 mg fenofibrate orally every day with meals are the first-line choice for isolated hypertriglyceridemia or mixed hypercholesterolemia plus hypertriglyceridemia.

In our opinion, an isolated increase of triglycerides with normal HDL values needs treatment only when levels of 1000 mg/dl are reached and the consequent risk of pancreatitis becomes high. In this situation, we recommend the replacement of saturated fats with non-saturated fats, and the addition of statin or fibrate drugs if diet change is ineffective. In combined disorders (high cholesterol, high triglycerides), statins and fibrates together may control lipid metabolism, but may also cause muscle damage (rhabdomyolysis). In some subjects, gemfibrozil (600 mg twice daily), atorvastatin (10 mg every day) or their combination causes a total cholesterol reduction of 32%, 19% and 30%, respectively, and a triglyceride reduction of 59%, 21% and 60%, respectively.

Interactions between antiretroviral compounds, lipid-lowering agents and hypoglycemic drugs are not clear. What is known is that many of these drugs are at risk of toxicity because the majority of them (atorvastatin, lovastatin, simvastatin, bezafibrate, ciprofibrate, fenofibrate, gemfibrozil) are metabolized by the same CYP3A liver enzymes as protease inhibitors and other drugs taken by HIV patients. Pravastatin and fluvastatin, on the contrary, have other mechanisms of excretion. Protease inhibitors, macrolides and imidazole derivatives have an inhibitory effect on CYP3A and can raise the levels of some statins 10-fold to 20-fold, potentially leading to increased muscle and liver toxicity with elevation of creatine phosphokinase (CPK) and alanine aminotransferase (ALT).

CHD due to elevated lipids or diabetes require 5–10 years to develop, while myocardial infarctions seen after a few weeks or months of HAART are usually attributed to thrombosis and not to atherosclerosis.

The use of metformin can reduce central fat and insulin resistance [41] but also reduces general fat and muscle mass. Troglitazone (400 mg/day) may normalize the glucose levels but no effects on lipids and body fat are observed [42]. Troglitazone (Rezulin) was removed from the market in March 2000 because of severe hepatocellular toxicities. Rosglitazone (Avandia) and pioglitazone (Actos) are related compounds with a lower risk of hepatocellular injury [43]. Growth hormone [39,40,44] reduces abdominal fat without influence on peripheral fat loss and lipids. Androgenic anabolic steroids (oxandrolone, nandrolone decanoate) increase muscular body mass without changes in lipids and body fat [45]. Niacin (nicotinic acid or vitamin B3) (50–100 mg orally twice daily/three times daily) and bile acid sequestring agents may have side effects, while

3–5 g fish oil orally every day is well tolerated [46]. We usually administer fish oil and/or vegetable derivative polyunsaturated fatty acids (PUFA) [22,45,47], associated with L-carnitine, to increase beta-oxidative processes of long-chain fatty acids and replace saturated fats with polyunsaturated fats. Physical exercise is prescribed to partly compensate the reduction of peripheral fat tissue with muscle mass hypertrophy [28,48,49]. In patients without other risk factors, such as smoking, pre-existing cardiovascular diseases, and lipid abnormalities, a wait-and-see attitude may be an appropriate strategy [14].

Exercise

Exercise has been extensively studied in patients with known coronary artery disease. It has been shown to have beneficial effects on the cardiovascular system as well as on the peripheral musculature [48,50–52]. Aerobic exercise and resistance exercise are the most popular methods to prevent or treat sarcopenia and to increase muscular performance [53].

In our experience, both aerobic and anaerobic exercise associated with a personalized training and diet program improve muscular endurance and body composition in HIV-infected patients [49,54]. All our exercise programs include progressive resistance training of the major muscle groups, which can be conditioned separately by specific exercises: the neck, arms and shoulders; the chest, abdomen and back; the buttocks; and the legs.

From an exercise perspective, it is encouraging that HDL cholesterol levels may be favorably increased in sedentary people who engage in aerobic training. Concurrently, the LDL cholesterol levels are lowered so the net result is an improved ratio of HDL cholesterol to LDL cholesterol, or HDL cholesterol to total cholesterol. This exercise effect appears to be independent of whether the diet is low in fat or whether the exerciser is overweight. The effect of regular endurance-type exercise on blood lipid profile is certainly a strong argument for incorporating vigorous physical activity into a total program of health maintenance in HIV-infected patients receiving HAART. Exercise improves myocardial circulation and metabolism that protects the heart from hypoxic stress [53]. Vascularization, cardiac glycogen stores and glycolytic capacity are enhanced, conditions that could be beneficial when the heart's oxygen supply is compromised. Mechanical and contractile properties of the myocardium are improved, enabling the conditioned heart to maintain or increase contractility during a specific challenge. Heart rate and blood pressure are favorably reduced so the work of the myocardium is significantly reduced at rest and during exercise.

Exercise reduces symptoms and medication requirements, corrects nutritional imbalance, side effects of drugs and altered diet. Many clinical signs and symptoms are responsive to exercise: atrophy of muscle and bone, postural hypotension, joint stiffness, reflexes, cardiovascular deconditioning, anorexia, gastrointestinal motility, insomnia and depression. Exercise is the way to stimulate the muscles not only to better spacially move the body, but also to increase biochemical reactions devoted to produce energy. The predominant energy pathways required in physical activities are the adenosine triphosphate-creatine phosphate (ATP-CP) system, the lactic acid system, and the oxygen or aerobic system that are often operative simultaneously. However, their relative contributions to the total energy requirement during an exercise may differ markedly. This contribution is related directly to the length of time a specific activity is performed and its intensity.

Anaerobic conditioning

With an intense maximum burst of energy lasting a maximal time of 6 s, the energy is provided anaerobically and supplied almost exclusively by the stored high-energy molecules of phosphates, ATP and CP. Maximum overload of the phosphate pool can be achieved by engaging specific muscles in maximum bursts of effort for 5 or 10 s. In training to enhance the ATP-CP energy capacity of specific muscles, the subject should undertake numerous bouts of intense, short-duration exercise. In a performance that lasts between 10 and 90 s, the energy is still supplied predominantly by anaerobic reactions, but the energy from lactic acid production plays a much more important role. To improve capability for more prolonged anaerobic energy release via the lactic acid energy system, the training program for such activities must be of sufficient intensity and duration to stimulate lactic acid production as well as to overload the ATP-CP energy system. Repeat bouts of up to 1 min maximum running, swimming or cycling stopped 30–40 s before exhaustion will cause lactic acid to increase to near maximum levels and overload this energy system. The exercise activity should be repeated several times after 1 to 2 min of recovery. When the body produces large amounts of lactic acid, recovery time from the exercise can be considerable.

Aerobic conditioning

After 2–4 min of continuous exercise, any physical activity becomes progressively more dependent on aerobic energy for the re-synthesis of the phosphates.

Under aerobic conditions, pyruvic acid from carbohydrate metabolism and molecules from fat and protein are transformed in various intermediate substances, with the final formation of CO_2, H_2O and large amounts of energy. If the O_2 supply and utilization are adequate, the lactic acid does not accumulate and fatigue will be absent. If one can reach a condition of endurance or aerobic fitness, the body is able to generate the necessary O_2 supply.

ATP aerobically exceeds the energy produced from anaerobic reactions. To have an adequate measure of cardiovascular capacity, we use the 'step up' test that provides the heart rate response to aerobic exercise: a low heart rate during exercise and a small increment with more intense exercise reflect a high level of cardiovascular fitness. A simple method to recover heart rates for evaluation of relative fitness for aerobic exercise is the Techumseh step test [50]. The stepping cadence must be 22 steps/min for women and 24 steps/min for men, with a stepping height of 20 cm. At the completion of 3 min of stepping, the subject remains standing; and exactly 30 s after stopping, the pulse is measured for 30 s more. The number of pulse beats from 30 s after stepping to the 1 min post-exercise period is the heart rate score. From the step test recovery heart rate, we can calculate the maximal O_2 consumption [51].

Frequency, duration and intensity of training

A training response occurs if exercise is performed two or, preferably, three times each week for at least 6 weeks. Both continuous as well as intermittent overload are effective in improving aerobic capacity. A single 3–5 min of vigorous exercise performed three times per week improves aerobic capacity as a less exhausting but steady-state exercise for 20 min. Intensity of training is the most critical factor related to successful aerobic conditioning and can be expressed as calories consumed, as a percentage of maximal O_2 consumption, as heart rate or as multiples of the RMR required to perform the exercise. The intensity of training must be sufficient to produce an increase in heart rate to at least 130–140 beats/min, equivalent to about 50–55% of the maximum aerobic capacity or about 70% of the maximum exercise heart rate. Our aerobic training program is conducted 3 days per week utilizing 20–30 min of continuous exercise of sufficient intensity to expend about 300 kcal. For example, subjects trained on a bicycle ergometer for 20 min/day, three times per week for 8 weeks, with a training intensity of 85% of the maximum heart rate, improved by 7.8% maximal O_2 uptake.

For developing a complete muscular strength, three exercise systems are commonly used: weight training, isometric training and isokinetic training.

Conclusions

In conclusion, the present paper outlines major changes in metabolic profiles and body shape and fat distribution in HIV-infected patients receiving HAART, as well as their role in raising cardiovascular risk in these patients. Dietary and pharmacological interventions are established to reduce metabolic changes and the relevant risk. Dietary counseling aimed at keeping an adequate nutrient and essential fatty acid intake is routinely offered. Diet supplementation with fish oil is prescribed when a suppression of lipid mobilization is desired. The use of antihyperlipidemic drugs should be reserved for patients at high risk of cardiovascular events. In patients with isolated hypertriglyceridemia who are not at high risk, its use should be limited to cases of severe hyperlipidemia (>1000 mg/dl) with increased risk of pancreatitis.

The potential for physical exercise to reduce such changes in HIV patients has been investigated. A training program that involves the use of weights, bicycle ergometer, isometric and isokinetic exercises was designed. This included both aerobic and anaerobic conditioning sufficient to reach about 50–55% of the maximum aerobic capacity or about 70% of the maximum exercise heart rate. Our conclusions are that such a program may substantially contribute to the control of metabolic changes, even reducing the requirement for antihyperlipidemic drugs. It is hypothesized that these interventions may lower the incidence of cardiovascular events in these patients. The role of a well-planned exercise program should therefore be emphasized and used as medical treatment among patients and health care professionals.

Sponsorship: This work was supported by the Istituto Superiore di Sanità, Rome, University of Pavia and IRCCS Policlinico S. Matteo, Pavia, Italy.

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