REVIEW ARTICLE

HIV-ASSOCIATED LIPODYSTROPHY AND EXERCISE

Mutimura E[1], Stewart A, PhD[2], Crowther NJ, PhD[3]

[1] PhD Candidate and Lecturer, Kigali Health Institute, Department of Physiotherapy, Kigali-Rwanda.
[2] Associate professor, The University of the Witwatersrand, Department of Physiotherapy.
[3] Associate professor, The University of the Witwatersrand, Department of Chemical Pathology.

ABSTRACT: *As individuals affected by HIV/AIDS live longer due to the availability of HAART, the challenge to health care professionals is to manage and alleviate abnormalities associated with HAART. HIV lipodystrophy- altered body fat redistribution- is the most common stigmatising physical abnormality related to the use of HAART, which may be alleviated by exercise participation. Currently, there is no reliable management standard care for HIV-associated lipodystrophy. However, there is sufficient evidence to support the benefits of exercise in adults with HIV infection. As various types of ARTs become available in the most HIV/AIDS stricken developing countries, there are inadequate studies to evaluate and promote exercise in alleviating HIV lipodystrophy and other related complications. The current paper reviews HIV-related lipodystrophy, related metabolic dysfunction, and the role of exercise in its management. The paper highlights the need to evaluate the effectiveness of exercise on HIV lipodystrophy syndrome. An emphasis needs to be put on raising awareness among health care professionals in Sub-Saharan Africa where the prevalence of HIV/AIDS is the highest in the world.*

KEY WORDS: EXERCISE, HAART, HIV, LIPODYSTROPHY, METABOLIC FUNCTION.

INTRODUCTION

The management of Human Immune-deficiency Virus (HIV) infection and development of Acquired Immune Deficiency Syndrome (AIDS) has evolved since the syndrome was first described. The trend is changing as various types of Anti-Retroviral Therapies (ARTs) are already in use. In particular, the use of Highly Active Antiretroviral Therapy (HAART) has improved the survival rate of individuals affected by HIV/AIDS (Scevola et al 2003). Despite the significant achievement, the use of HAART may compromise the quality of life (QOL) of individuals using this type of therapy due to new emerging abnormalities (Carr et al 1999). Lipodystrophy, the most common morphologic HAART-associated abnormality results in altered fat distribution (Chang et al 2002). Most affected individuals experience lipo-hypertrophy or abnormal fat increases in the abdomen, resulting in protuberant pot-like bellies (Carr et al 2003). Fat increases in the dorso-cervical region of the neck- 'the buffalo hump'- and breast enlargement are also common (Calza et al 2003). Lipoatrophy or loss of subcutaneous fat affects the arms and legs and results in the appearance of prominent veins on the extremities. Loss of fat also causes flattening of the buttocks, and loss of facial fat leads to sunken cheeks (Tershakovec et al 2004). The most common HAART-related metabolic complications include insulin resistance and dyslipidaemia (Calza et al 2003). The combination of morphologic and metabolic changes has been referred to as HIV lipodystrophy syndrome (Robinson 2004). The syndrome predominantly results in increased total cholesterols (TC), low density lipoproteins (LDL), triglycerides (TGs) and glucose levels and decreased high density lipoproteins (HDL) (Koutkia and Grinspoon 2004).

The core aim of this review seeks to increase the awareness of the need for exercise research in the management of HIV metabolic complications associated with the use of HAART. The current paper focuses on HIV-lipodystrophy, its aetiology, clinical consequences and possible management. The emphasis is to evaluate and promote exercise as a possible management strategy to alleviate HIV lipodystrophy and the related metabolic abnormalities.

CORRESPONDENCE TO:
E Mutimura
Kigali Health Institute,
Department of Physiotherapy,
B.P 3286
Kigali-Rwanda
Tel: 09250 08769615
Email: eumuran@yahoo.co.uk

The Aetiology of Lipodystrophy

There is no conclusive evidence of the aetiology of lipodystrophy. However, a high number of cases of HIV-related lipodystrophy occurred immediately after the widespread use of Protease Inhibitors (PIs). The use of PIs (Carr et al 1999) and Nucleoside Reverse Transcriptase Inhibitors (NRTIs) have both been associated with HIV lipodystrophy and the related metabolic dysfunction (Galli et al 2002). However, it should be noted that lipodystrophy was observed even before the widespread use of PIs and NRTIs (Tershakovec et al 2004). The main initiators of lipodystrophy syndrome appear to be specific to the virus itself, effects of the types and duration of HAART used, genetic predisposition, gender and age (Galli et al 2002).

There are various hypothesized pathophysiological mechanisms of lipodystrophy syndrome. Carr et al (1998) have suggested a high homology of PIs and human proteins responsible for lipid metabolism, namely cytoplasmic retinoic acid binding protein type 1 (CRABP-1) and perioxisome-proliferator- activated receptor type gamma (PPAR-γ). The resultant combination of cis-9 retinoic

acid forms a complex (RXR: PPAR-γ) which inhibits peripheral adipocyte proliferation and differentiation (Robinson 2004). The use of NRTIs has been associated with mitochondrial toxicity resulting in depletion of mitochondrial DNA (mtDNA) due to inhibition of DNA polymerase gamma, the enzyme responsible for the synthesis of mtDNA (Brinkman et al 1999). Since mtDNA is responsible for encoding oxidative phosphorylation chain proteins, reduced mtDNA may prevent aerobic respiration and other mtDNA functions. Although a causal relationship needs yet to be established, this hypothesis is supported by structural changes observed in the subcutaneous fat biopsies of and subsequent mtDNA decrease in patients with HIV lipodystrophy (Walker et al 2002). Nevertheless, these hypotheses do not offer a comprehensive description of the aetiology of lipodystrophy since they do not account for signs of the syndrome in naïve HAART users. This perhaps suggests that alternative mechanisms for the pathophysiology of HIV lipodystrophy syndrome exist.

CLINICAL CONSEQUENCES

Lipodystrophy is increasingly becoming so common that patients on HAART can be identified as being HIV infected simply by their physical appearance (Robinson 2004). Therefore, it is becoming clearer that lipodystrophy-related physical changes are as stigmatising as the wasting and skin lesions in the earlier years of the epidemic (Scevola et al 2003). These physical abnormalities have sometimes resulted in low self-esteem, depression and other related psycho-social disturbances (Power et al 2003). Individuals on HAART with lipodystrophy have reported poor body image, decreased sexual relationships, inability to conceal HIV status and disruption of daily activities of living (Blanch et al 2004). Therefore, these physical abnormalities may deter treatment initiatives and discourage adherence to HAART (Power et al 2003). The latter situation can lead to antiretroviral resistant virus, uncontrolled viraemia or both (Schambelan et al 2002).

The occurrence of lipodystrophy has often been associated with elevated cholesterols (HDL decreases), triglycerides and glucose levels (Carr et al 2003). The occurrence of insulin resistance and hyperlipidaemia in abdominally obese subjects is a common feature of human obesity also observed in HIV negative subjects and is termed the metabolic syndrome or syndrome X (Koutkia and Grinspoon 2004). This may predispose individuals with lipodystrophy to chronic diseases including but not limited to premature coronary heart disease, myocardial infarction, peripheral arteriosclerosis, pancreatitis and cutaneous xanthomas (Calza et al 2003). The effects of lipodystrophy also include musculo-skeletal disorders, such as neck pain and back pain resulting from fat accumulation around the neck and breast enlargement, respectively. Due to spinal postural changes, severe fat deposition in the abdomen can further result in neck pain, and make it difficult to breath (Klemack, 2004).

EXERCISE AND HIV INFECTION

Aerobic exercise participation has been shown to improve certain components of cellular immunity, such as increasing CD4 cell counts by an average of 50 counts/m3 (LaPerriere et al 1991). These improvements are comparable to those observed in studies on AIDS risk groups using azidothymidine. In addition exercise increases neuromuscular strength and cardiorespiratory fitness in HIV positive patients (Rigsby 1992). Supervised exercise training improves cardiopulmonary fitness in HIV-infected persons indicated by increases in maximal oxygen (O_2) consumption (MaCarthur et al 1993). Aerobic exercise has also been indicated to improve cardiopulmonary functioning in asymptomatic HIV infected individuals (Perna et al 1999). Supervised aerobic exercise training can also reduce fatigue, weight, subcutaneous and abdominal fat in HIV individuals (Smith et al 2001). The substantial benefits of aerobic exercise such as increased aerobic fitness are not accompanied by changes in the immune system (Stringer et al 1998). However, during treadmill testing of HIV infected adolescents, Cade et al (2002) reported reductions in peak O_2 consumption, treadmill duration, peak treadmill stage and peak O_2 pulse. This indicated that aerobic capacity was substantially reduced in physically inactive adolescents with HIV infection compared to age-matched sedentary controls. This aerobic impairment capacity appears to be due to decreased peripheral tissue O_2 extraction (Cade et al 2003a) resulting from HIV infection, inflammation, type and duration of HAART or a combination of these factors. Furthermore, Cade et al (2003b) examined aerobic capacity of three study groups (n=39) during sub-maximal exercise testing. The authors reported a significant change in O_2 consumption in HIV participants on HAART, and HIV participants not taking HAART compared to the controls. Besides, there was a decrease in the ratio of the change in O_2 consumption to the mean response time (oxidative response index) in HIV participants on HAART, and HIV participants not taking HAART compared to controls. They concluded that impaired aerobic capacity indicated by a decrease in the rate of O_2 consumption was due to HIV infection rather than the use of HAART.

EXERCISE AND HIV LIPODYSTROPHY

Exercise has an important role in the management of chronic conditions, such as cancer (Demeo et al 1998), hypertension (Fish et al 1997) and hyperlipidaemia (Halbert et al 1999). Lipid metabolism, glucose tolerance and insulin sensitivity are among the main metabolic functions affected in HIV lipodystrophy syndrome (Carr et al 1999; Calza et al 2003), which may be improved by exercise participation (Yarasheski et al 2001). Both resistance exercise and aerobic exercise have been indicated to reduce anthropometric and metabolic risk factors for CAD (Yarasheski et al 2001; Jones et al 2001), in subjects with HIV lipodystrophy syndrome. Despite these positive effects of aerobic exercise, few large studies have been performed on the role of exercise as a primary treatment strategy for HIV-associated lipodystrophy and the related metabolic abnormalities (Robinson 2004). This can largely be attributed to lack of sufficient sample sizes and methodological difficulties in carrying out such studies. More recently however, Thöni et al (2002) indicated that light supervised aerobic exercise for 16 weeks decreased total adipose tissue, reduced low density lipoprotein (LDL) and total cholesterol (TC) while increasing high density lipoprotein

(HDL) levels. Furthermore, Jones et al (2001) demonstrated similar findings among six HIV patients with lipodystrophy who underwent an exercise programme for 10 weeks, in which there was improved aerobic exercise tolerance, body composition and blood lipid profiles. Resistance exercise training has also been effective in increasing muscle strength and clearance of serum triglycerides among HIV infected men on HAART (Yarasheski et al 2001). In a pilot study involving 10 HIV infected men who underwent 16 weeks of exercise training, reduction in trunk fat mass and increase in total body mass was reported. Exercise participation was three times a week, and comprised of aerobic exercises (20 minutes) and resistance exercises (high intensity lifting for about 60 minutes) (Roubenoff et al 1999).

These findings can be substantiated further by randomised control trials with larger subject numbers and longer duration exercise training. Based on the data from previous pilot studies, interventions to evaluate the effectiveness of exercise in the management of lipodystrophy syndrome and the associated metabolic complications are warranted.

REFERENCES

Blanch J, Rousaud A, Martinez E, De Lazzari E, Milinkovic A, Peri J M, Blancho J L, Jaen J, Navarro V, Massana G and Gatell J 2004 Factors Associated with Severe Impact of Lipodystrophy on Quality of Life of Patients Infected with HIV-1. Clinical Infectious Diseases 38: 1464-1470

Brinkman K, Smeitink JA, Romijn JA and Reiss P 1999 Mitochondrial toxicity induced by nucleoside-analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral-therapy-related lipodystrophy. Lancet 354: 1112-1115

Cade WT, Peralta L and Keyser RE 2002 Aerobic capacity in late adolescents infected with HIV and controls.Paediatric rehabilitation 5: 161-169

Cade WT, Fantry LE, Nabar S and Keyser RE 2003a Decreased peak arteriovenous oxygen difference during treadmill exercise testing in individuals infected with the human immuno deficiency virus. Achives of Physical Medicine and Rehabilitation 84: 1595-1603

Cade WT, Fantry LE, Nabar S and Keyser RE 2003b Impaired oxygen on-kinetics in persons with the human immunodeficiency virus are not due to highly active antiretroviral therapy. Achives of Physical Medicine and Rehabilitation 84: 1831-1838

Calza L, Manfred R and Chiodo F 2003 Hyperlipidaemia in patients with HIV-1 infection receiving Highly Active Antiretroviral Therapy: epidemiology, pathogenesis, clinical course and management. International Journal of Antmicrobial Agents 22: 89-99

Carr A, Emery S, Law M, Puls R, Lundgren JD and Powderly WG 2003 An Objective case definition of lipodystrophy in HIV-infected adults: a case-control study. The Lancet 361: 726-735

Carr A, Samaras K, Thorisdottir A, Kaufmann GR, Chisholm DJ and Cooper DA 1999 Diagnosis, prediction, and natural course of HIV-1 protease inhibitor associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. The Lancet 353: 2093-2099

Dimeo F, Rumberger BG and Kaul J 1998 Aerobic Exercise as a Therapy for Cancer Fatigue. Medical Science of Sports Exercise 30: 475-478

Fish AF, Smith BA, Frid DJ, Christmas SK, Post D and Montalto NJ 1997 Step Treadmill exercise training and blood pressure reduction in women with mild hypertension. Progressive Cardiovascular Nursing 12: 28-35

Galli M, Ridolfo AL, Adorni F, Gervasoni C, Ravasio L, Corsico L, Gianelli E, Piazza M, Vaccarezza M, Monforte A, Moroni M 2002 Body Habitus changes and metabolic alterations in protease inhibitor-naïve HIV-1 infected patients treated with two nucleoside reverse transcriptase inhibitors. Journal of Aquired Immune Deficiency Syndrome 29: 21-31

Halbert JA, Silagy CA, Finucane P, Withers RT and Hamdorf PA 1999 Exercise Training and Blood Lipids in Hyperlipidemic and Normolipidemic Adults: A meta-analysis of randomised controlled trials. European Journal of Clinical Nutrition 53: 514-522

Jones SP, Doran D, Leatt PB, Maher B and Pirmohamed M 2001 Short-term exercise training improves body composition and hyperlipidaemia in HIV-positive individuals with lipodystrophy. AIDS 15: 2049-2051

Klemack C 2004 Benefits of Exercise for People with HIV/AIDS. National Center on Physical activity and disability.www.ncpad.org/whtpprs/klemackAIDSpaper.htm -8th January 2005

Koutkia P and Grinspoon S 2004 HIV- Associated Lipodystrophy: Pathogenesis, Prognosis, Treatment, and Controversies 55: 303-317

LaPerriere MA, Fletcher MH, Antoni NG, Klimas I and Schneiderman N 1991 Aerobic Exercise Training in AIDS risk group. International Journal of Sports Medicine S53-S57

MaCarthur RD, Levine SD and Birk TJ 1993 Supervised Exercise Training improves cardiopulmonary fitness in HIV infected persons. Medicine Science Sports Exercise 25: 684-688

Perna FM, LaPerriere A, Klimas N, Ironson G, Perry A, Pavone J, Goldstein A, Majors P, Makemson D, Talutto C, Scheiderman N, Fletcher MA, Meijer OG, Koppes L 1999 Cardiopulmonary and CD4 cell changes in response to exercise training in early symptomatic HIV Infection. Medicine Science Sports Exercise 31: 973-979

Power R, Tate H L, McGill S M and Taylor C 2003 A qualitative study of the psychosocial implications of lipodystrophy syndrome on HIV positive individuals. Sexual Transmission Infection 79: 137-141

Rigsby LW, Distiman RK, Jackson AW, Maclean GS and Raven PB 1992 Effects of exercise training on men seropositive for the human immunodeficiency virus-1. Medicine and Science in Sports & Exercise 24: 6-12

Robinson P 2004 HIV Lipodystrophy: A Primer. Journal of the association of Nurses in AIDS Care 15: 15-19

Roubenoff R 1999 A pilot study of exercise training to reduce trunk fat in adults with HIV-associated fat redistribution. AIDS 13: 1373-1375

Scevola D, Di Matteo A, Lanzarini P, Uberti F, Scevola S, Bernini V, Spoladore G and Faga A 2003 Effect of Exercise and Strength training on Cardiovascular Status in HIV- infected patients receiving highly active antiretroviral therapy. AIDS 17: 123-129

Schambelan M, Benson CA, Carr A, Currier JS, Dube MP and Gerber JG 2002 Management of Metabolic complications associated with antiretroviral therapy for HIV -1 infection: Recommendations of an International AIDS Society-USA panel. Journal of Acquired Immune Deficiency Syndrome 31: 257-275

Smith B, Neidig J, Nickel J, Mitchell G, Para M and Fass RJ (2001) Aerobic exercise: effects on parameters related to fatigue, dyspnea, weight and body composition in HIV-infected adults. AIDS 15: 693 -701

Stringer WW, Berezovskaya M, O'Brien W A, Beck CK and Casaburi R 1998 The effect of exercise training on aerobic fitness, immune indices, and quality of life in HIV+ patients. Medicine & Science in Sports and Exercise 30: 11-16

Tershakovec AM, Frank I, and Rader D 2004 HIV-related lipodystrophy and related factors. Atherosclerosis 174: 1-10

Thoni GJ, Fedou C, Brun JF, Fabre J, Renard E, Reynes J, Varray A and Mercier 2002 Reduction of Fat Accumulation and Lipid Disorders by Individualized Light Aerobic Training in HIV Infected Patients with Lipodystrophy and or Dyslipidaemia. Diabetes Metabolism 28: 397-404

Walker UA, Bickel M, Lutke VS, Ketelsen UP, Schofer H, Setzer B, Venhoff N, Rickerts V, Staszewski S 2002 Evidence of Nucleoside analogue reverse transcriptase inhibitor-associated genetic and structural defects of mitochondria in adipose tissue of HIV-infected patients. Journal of Acquired Immune-deficiency Syndrme 29: 117-121

Yarasheski KE, Tebas P, Stanerson B, Claxton S, Marin D, Bae K, Kennedy M, Tantisirwat W and Powderly WG 2001 Resistance Exercise Training Reduces Hypertriglyceridemia in HIV-infected men treated with anti-Retroviral Therapy. Journal of Applied Physiology 90: 133-138