HIV-ASSOCIATED LIPODYSTROPHY AND EXERCISE

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). Lipatrophy 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.

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 peroxisome 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 cholesterol (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 atherosclerosis, pancreatitis and cutaneous xanthomas (Calza et al 2003). The effects of lipodystrophy also include musculoskeletal 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 (O2) consumption (MacArthur et al 1993). Aerobic exercise has also been indicated to improve cardiopulmonary functioning in asymptomatic HIV infected individuals (Perma 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 O2 consumption, treadmill duration, peak treadmill stage and peak O2 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 O2 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 O2 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 O2 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 O2 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 (Deno 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, exercise training has been shown to improve insulin tolerance in HIV lipodystrophy patients (Yarasheski et al 2001). Additional clinical studies are necessary to further investigate the role of exercise in the treatment of HIV lipodystrophy syndrome.
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