HIV Lipodystrophy Syndrome: A Primer

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Treatment with highly active antiretroviral therapy (HAART) has been implicated in the development of anthropomorphic and metabolic abnormalities termed HIV lipodystrophy syndrome (or LDS). This primer offers a comprehensive overview of LDS including epidemiology, hypothesized etiologies, and clinical consequences. The evidence-based literature is reviewed for current treatment strategies including discontinuation of specific antiretrovirals, pharmacological management of dyslipidemia and insulin resistance, exercise training, facial augmentation, liposuction, and hormonal therapy. Patient education, counseling, and adherence are discussed.

Key words: lipodystrophy, HIV/AIDS, metabolic abnormalities, antiretroviral therapy

In HIV disease, highly active antiretroviral therapy (HAART) causes dramatic and sustained suppression of viral replication, improves immune function, and reduces morbidity in individuals (Chiesi et al., 1999; Palella et al., 1998). However, a constellation of negative anthropomorphic and metabolic abnormalities (referred to as lipodystrophy syndrome or LDS) has been commonly recognized in individuals receiving HAART. Anthropomorphic findings have included lipo hypertrophy (fat accumulation) in the abdomen, breasts, and dorso-cervical region (“buffalo hump”) and lipoatrophy (wasting) in the face, arms, legs, and buttocks (Carr, Samaras, Chisholm, & Cooper, 1998a; Dong et al., 1999; Heath, Hogg, et al., 2002; Ridolfo, Gervasoni, Bini, & Galli, 2000; Safrin & Grunfeld, 1999; Saint-Marc et al., 2000). Furthermore, multiple imaging studies have confirmed that the abdominal lipo hypertrophy is in the visceral as opposed to subcutaneous depot (Kosmiski et al., 2001; K. D. Miller et al., 1998; Saint-Marc et al., 2000; Shevitz, 2001). Metabolic findings generally seen in LDS include insulin resistance and hyperinsulinemia (Carr, Samaras, Burton et al., 1998; Carr, Samaras, Chisholm, & Cooper, 1998b; Carr et al., 1999; Hadigan, Corcoran, Stanley, et al., 2000; Hadigan et al., 1999; Mulligan et al., 2000; Walli et al., 1998; Yarasheski et al., 1999) and dyslipidemia (elevation of serum LDL cholesterol and triglycerides with reduction of HDL cholesterol) (Berthold et al., 1999; Carr, Samaras, Burton, et al., 1998; Carr et al., 1999; Dong et al., 1999; Koppel, Bratt, Eriksson, & Sandstrom, 2000; Mulligan et al., 2000; Penzak & Chuck, 2000; Tsiodras, Mantzoros, Hammer, & Samore, 2000; Vergis, Paterson, Wagener, Swindells, & Singh, 2001).

Other metabolic abnormalities such as accelerated bone mineral loss have been associated with HAART. However, its relationship to LDS is unclear. For example, osteopenia and osteoporosis were found to be associated with (Huang, Rietschel, Hadigan, Rosenthal, & Grinspoon, 2001) and independent from (Tebas et al., 2000) fat redistribution in patients on HAART (PI [protease inhibitor] and nonPI regimens). Furthermore, equivalent rates of osteopenia were found in patients pre- and post-HAART era (Lawal, Engelson, Wang, Heymsfield, & Kotler, 2001) and between patients on HAART and antiretroviral naive patients (Huang et al., 2001; Knobel, Guelar, Vallecillo, Nogues, & Diez, 2001), suggesting that...
HIV itself may be the most prominent risk factor for bone loss.

There are no definitive diagnostic criteria for LDS, rather the term has emerged as a convenient organizing term for the aforementioned abnormalities. However, it is unclear, and a matter of some controversy, whether the anthropomorphic and metabolic findings represent separate conditions or various stages of a single syndrome (Ridolfo et al., 2000; Shevitz, 2001).

**Epidemiology of LDS**

The prevalence of LDS among HIV-infected individuals varies widely, possibly because of variations in study methodology, sample selection, defining criteria, and outcome measurement techniques (Heath, Hogg, et al., 2002; Safrin & Grunfeld, 1999). A recent prospective population-based study (n = 745) concluded that approximately 50% of patients show at least one sign of LDS within 1 year of initiation of HAART—PI and non-PI regimes (Heath, Hogg, et al., 2002). Another cohort study (Galli et al., 2002) that followed 655 patients from initiation of HAART (50% on PI regimens) found that 20% manifested some form of fat redistribution within 2 years. Other estimates of fat redistribution abnormalities are as high as 84% of individuals receiving a PI (Carr et al., 1999). The prevalence of dyslipidemia approaches 60% with PI treatment and is relatively high in HIV-infected individuals (15%-30%) in general (Struble & Piscitelli, 1999). Impaired glucose tolerance due to insulin resistance has been shown to be as high as 35% in HAART-treated individuals with evidence of fat redistribution (Hadigan et al., 2001).

Investigators have identified distinct phenotypes of LDS: primarily central lipohypertrophy or peripheral lipoatrophy or a combination (Ridolfo et al., 2000; Saint-Marc et al., 2000). Note that these phenotypes are based only on fat redistribution and not metabolic abnormalities. Some gender-based differences in presentation have also been reported, with men more likely to develop lipoatrophy and women lipohypertrophy (Schambelan et al., 2002). Levels of dyslipidemia and insulin resistance vary across the phenotypes with great interindividual variability (Saint-Marc et al., 2000). Two prospective studies (Heath, Chan, et al., 2002; Heath, Hogg, et al., 2002) investigated incidence of these phenotypes. In a sample of 745 participants on HAART who were followed for 1 year (Heath, Hogg, et al., 2002), incidence was 21% for lipohypertrophy, 27% for lipoatrophy, 10% for elevated triglycerides, and 17% for elevated cholesterol. Similarly, among 366 participants who were followed from HARRT initiation for a median duration of 1 year (Heath, Chan, et al., 2002), cumulative incidence was 23% for lipohypertrophy, 29% for lipoatrophy, 13% for combined lipodystrophy, and 9% for increased triglycerides or cholesterol. Furthermore, the occurrence of lipid abnormalities and fat redistribution were independent, with those having fat redistribution at no greater risk of concomitant lipid disturbance. An additional study of 655 participants that looked only at fat redistribution (Galli et al., 2002) found the following site-specific results: abdominal fat accumulation (10%), enlarged breasts (2%), loss of lower limb fat (7%), and loss of facial fat (4%). This study also noted that lipohypertrophy occurred earlier than lipoatrophy (regardless of site) for the sample.

**Hypothesized Etiologies of LDS**

The etiology of LDS remains unknown, but the recognition of LDS occurring temporally after the widespread use of HAART has led to suspicion that it is a manifestation of drug toxicity (Kotler, Rosenbaum, Wang, & Pierson, 1999). It has been consistently attributable to the use of PIs (K. D. Miller et al., 1998; Periard et al., 1999; Roth, Kravcik, & Angel, 1998; Stein et al., 2001; Vergis et al., 2001; Walli et al., 1998). However, metabolic and anthropomorphic abnormalities were described in HIV-infected individuals prior to the introduction of PIs (Grunfeld et al., 1989; Sellmeyer & Grunfeld, 1996) as well as in individuals on PI-sparing HAART regimes (Carr, Samaras, Burton, et al., 1998; Carr et al., 1999; Lo, Mulligan, Tai, Algren, & Schambelan, 1998; Madge, 1999; Mallal, John, Moore, James, & McKinnon, 2000; Mulligan et al., 2000; Penzak & Chuck, 2000; Periard et al., 1999; Saint-Marc et al., 1999; Yanovski, 1999). Thus, nucleoside reverse transcriptase inhibitor (NRTI) therapy has also been hypothesized to be an etiological factor in some of the manifestations of LDS (Carr, Samaras, Burton, et al., 1998; Heath et al., 2001; Saint-Marc et al., 1999).
Several pathophysiological mechanisms underlying LDS have been implicated. Carr, Samaras, Chisholm, et al. (1998b) proposed a direct effect of PIs on lipid metabolism because of a high degree of homology between HIV protease and two human proteins involved in lipid metabolism. During normal lipid metabolism, one protein, cytoplasmic retinoic-acid binding protein type 1 (CRABP-1), binds intracellular retinoic acid and presents it to the cytochrome P450 enzymes forming cis-9 retinoic acid that then functions as a ligand to bind retinoid X receptor (RXR) and peroxisome-proliferator-activated receptor type gamma (PPAR-γ). This complex (RXR:PPAR-γ) inhibits adipocyte apoptosis and causes an upregulation of adipocyte proliferation and differentiation. PIs bind to CRABP-1 (it contains an amino acid sequence that is 58% homologous to the catalytic region of HIV protease) and decrease the formation of RXR:PPAR-γ, which results in increased apoptosis of peripheral adipocytes and diminished adipocyte differentiation. Such events (stimulated lipolysis, inhibited lipogenesis) would explain hyperlipidemia, leading to decreased triglyceride storage and release of lipids into the bloodstream. Additionally, PPAR-γ is preferentially expressed in peripheral rather than central adipose, thus possibly explaining peripheral lipoatrophy. The other protein, low-density lipoprotein-receptor-related protein (LRP), shares 63% homology with HIV protease. When coexpressed with the lipolytic enzyme lipoprotein lipase (LPL) on capillary endothelium, the LRP:LPL complex cleaves fatty acids from triglycerides, thereby promoting free fatty acid storage in adipocytes. Carr and colleagues (1998b) hypothesize that PI-binding LRP would interfere with fatty acid storage by this mechanism and increase hyperlipidemia. Impaired storage of peripheral adipose by default might result in fat accumulation in the more central parts (visceral) of the body. Increases in visceral fat are associated with insulin resistance in HIV-infected and -uninfected individuals (Meininger, Hadigan, Rietschel, & Grinspoon, 2002), but PIs may also have a direct effect on inducing insulin resistance independent of changes in body adipose (Mulligan et al., 2000) by inhibiting glucose transporter-4, which is the predominant transporter involved in insulin-stimulated uptake of glucose.

Although PI hypotheses are plausible, they cannot account for signs of LDS in PI-naive individuals, suggesting alternate or at least additional pathogenic mechanisms. A direct effect of NRTIs (Brinkman, Smeitink, Romijn, & Reiss, 1999) that is related to mitochondrial toxicity has been proposed. It is well established that NRTIs can deplete mitochondrial DNA (mtDNA) in cell culture by inhibiting DNA polymerase gamma, the enzyme primarily responsible for the synthesis of mtDNA (Chen, Vazquez-Padua, & Cheng, 1991; Medina, Tsai, Hsiung, & Cheng, 1994). Through this mechanism, NRTIs could easily deplete mtDNA, resulting in depletion of mtDNA-encoded mitochondrial enzymes, thereby altering mitochondrial function. It should be noted, however, that consistent DNA rearrangements have yet to be found in mitochondria from individuals with LDS (McComsey, Tan, Lederman, Wilson, & Wong, 2002). Impaired mitochondria would result in decreased oxidative phosphorylation (aerobic metabolism via the respiratory chain) leading to disordered lipid metabolism. Mitochondrial toxicity currently is the leading hypothesis related to the lipoatrophy associated with LDS (Brinkman et al., 1999; Mallal et al., 2000; McComsey et al., 2002), and length of time on NRTIs is positively related to development of lipoatrophy (Galli et al., 2002). Lactic acidosis is another well-described mitochondrial toxicity of NRTI use (Chattha, Arieff, Cummings, & Tierney, 1993; Fortgang, Belitsos, Chaisson, & Moore, 1995), thus explaining its appearance with HAART. NRTI use is also associated with increased lipolysis, which may contribute to insulin resistance (Hadigan, Borgonha, Rabe, Young, & Grinspoon, 2002).

Additionally, the well-established process of HIV-related wasting syndrome may play a role in some of the manifestations of LDS such as peripheral lipoatrophy (Kotler et al., 1999). There also appears to be an association between development of LDS and effective virus control and immune reconstitution (Gervasoni et al., 1999; K. D. Miller et al., 1998). One possible mechanism related to this reversal of advanced HIV disease with HAART is dysregulation of proinflammatory cytokines that play a role in lipid metabolism. For example, elevated levels of tumor necrosis factor-alpha (TNF-α) and interferon-alpha (INF-α) have been associated with development and
worsening of LDS (Christeff, Melchior, de Truchis, Perronne, & Gougeon, 2002; Ledru et al., 2000; Mynarcik, McNurlan, Steigbigel, Fuhrer, & Gelato, 2000).

Furthermore, age, female gender, coinfection with hepatitis C, duration and severity of HIV disease, duration of immune recovery, and degree of prior immune suppression are positively related to development of LDS (Galli et al., 2002; Lichtenstein et al., 2001). Thus, the sum of the evidence suggests that the causes of LDS are multifactorial with the precise etiological mechanisms remaining unclear. It is likely that both PIs and NRTIs contribute to findings of LDS, with some evidence of a synergistic effect of the two accelerating the course of LDS (Mallal et al., 2000), but the drug’s effects seem to be modulated substantially by each individual’s history and underlying condition (Lichtenstein et al., 2001).

Any sequential pattern to the development of LDS is also obscure. Available evidence shows that increases in serum triglyceride levels preceede the detection of fat redistribution, but their reciprocal relationship is not clear because although dyslipidemia might promote fat redistribution, fat redistribution might contribute to worsening dyslipidemia (Carr, Samaras, Chisholm, et al., 1998b; Shevitz, 2001). Conversely, several studies contain evidence that fat redistribution is an important predictor of hyperinsulinemia and insulin resistance, with the most severe insulin abnormalities occurring in individuals with combined central lipohypertrophy and peripheral lipoatrophy (Grinspoon, 2001; Hadigan et al., 2001; Mynarcik et al., 2000).

Clinical Consequences Associated With LDS

LDS has multiple clinical consequences that may affect the quality of life and morbidity of HIV-infected individuals. First, LDS fat redistribution leads to a characteristic and easily identifiable appearance serving to further stigmatize HIV-infected individuals. Therefore, anthropomorphic abnormalities may present significant psychosocial challenges for individuals in terms of self-esteem. A survey on the psychosocial impact of LDS found that individuals with LDS had poor body image, low self-esteem, became socially withdrawn, found their sexual relationships were adversely affected, were unable to conceal their HIV status, and commonly were depressed (Collins, Wagner, & Walmsley, 2000). Such phenomena could discourage adherence to HAART and possibly deter treatment initiation (Schambelan et al., 2002; Shevitz, 2001), resulting in antiretroviral resistant virus, uncontrolled viremia, or both (Bangsberg et al., 2000; Deeks, 2000).

The abnormalities associated with LDS (except peripheral lipoatrophy) are consistent with the metabolic syndrome referred to as syndrome X (DeFronzo, 1992; Fagan & Deedwania, 1998; Reaven, 1988). This syndrome is predictive of accelerated atherosclerosis with progression to high risk for myocardial infarction, stroke, and peripheral vascular disease (Deedwania, 1998; DeFronzo, 1992; Fagan & Deedwania, 1998; Reaven, 1988). In general, epidemiologic, postmortem, genetic, and angiographic studies have demonstrated a causal relationship between elevated serum cholesterol levels, low HDL levels, and elevated triglyceride concentrations and the development of coronary artery disease (CAD) (Assmann & Schulte, 1992a, 1992b; Cleeman & Lenfant, 1998; Fedder, Koro, & L’Italien, 2002; Kannel, 1979; Levine, 1995; Manninen et al., 1992; Stampfer et al., 1996). Prospective, population-based studies have demonstrated that hyperglycemia (Donahue, 1987) and hyperinsulinemia (Lamarche et al., 1998) in nondiabetic individuals are associated with subsequent development of CAD. Central adiposity is also positively related to coronary atherosclerosis (Hodgson, Wahlqvist, Balazs, & Boxall, 1994; Thompson, Ryu, Craven, Kahl, & Crouse, 1991). The pathophysiology of CAD that can result from LDS is complex and multifactorial. In brief, from existing work in other populations, metabolic changes such as those occurring in LDS alter the function of multiple cell types including those of the endothelium, smooth muscle, and platelets resulting in vasoconstriction, inflammation, and thrombosis, leading to atherogenesis (Beckman, Creager, & Libby, 2002).

Thus, there is considerable evidence that individuals with LDS may be at risk for atherosclerotic CAD. Indeed, premature arteriosclerosis including infarction and need for revascularization has been associated with LDS and reported in individuals while on HAART (David, Hornung, & Fichtenbaum, 2002;
Duong et al., 2001; Gallet, Pulik, Genet, Chedin, & Hiltgen, 1998; Henry, Melroe, Huebesch, Hermundson, Levine, et al., 1998; Muise & Arbess, 2001; Sullivan, Nelson, et al., 1998). Furthermore, endothelial dysfunction (Stein et al., 2001), carotid intima thickening (Mercie et al., 2002), elevated subclinical coronary artery plaque burden (Acevedo et al., 2002), and elevated blood pressure (Sattler et al., 2001) have been associated with HAART, LDS, or both. The most compelling evidence for cardiovascular risk related to HAART comes from an ongoing prospective observational cohort of the HIV Outpatient Study (HOPS). In this cohort of 5,672, the frequency of myocardial infarctions (MI) increased after the introduction of the PIs in 1996 (19 of 3,247 taking, but only 2 of 2,425 not taking PIs had an MI) (Holmberg et al., 2002). Occurrence of an MI was significantly related to frank diabetes and hyperlipidemia (Holmberg et al., 2002). The profile of LDS and risks for CAD are emerging as major issues in the management of HIV disease, raising the possibility that treatment of one pathology (HIV disease) leads to another (CAD).

**LDS Treatment Strategies**

**Discontinuation of Specific Antiretrovirals**

As with any drug toxicity, discontinuation of the offending agent might be warranted (Geletko & ZuWallack, 2001), but in the case of antiretroviral agents, discontinuing drugs could lead to viral rebound and disease progression. Switching antiretrovirals is not an option for some individuals with LDS, owing to viral resistance profiles and impaired tolerance. In general, investigators who have examined the effect of switching individual PIs or substituting a nonnucleoside reverse transcriptase inhibitor (NNRTI) for a PI have found improvements in dyslipidemia and insulin resistance in LDS (Carr et al., 2001; Carr et al., 2002; Martinez, Conget, Lozano, Casamitjana, & Gatell, 1999; Martinez et al., 2000; Negredo et al., 2002; R. K. Walli, Michl, Bogner, & Goebel, 2001; Wensing, Reedijk, Richter, Boucher, & Borleffs, 2001). However, individuals in all these studies remained on NRTIs, known to be associated with various negative metabolic outcomes, and study follow-up was relatively short (7 months in most cases); therefore, the long-term effects of these substitution strategies are unknown.

**Pharmacological Treatment of LDS Components**

One potential strategy used to reduce risk of CAD in LDS is pharmacological management of dyslipidemia and insulin resistance, but any pharmacological agent adds to the excessive pill burden that is associated with HAART, making adherence more difficult. Statins and fibrates are the most commonly used lipid-lowering classes of drugs (Meienberg, Battegay, Bucher, & Battegay, 2001; Penzak & Chuck, 2000), and the limited clinical data that are available are suggestive that they are efficacious in lowering total cholesterol and triglycerides in LDS (Baldini et al., 2000; Henry, Melroe, Huebesch, Hermundson, & Simpson, 1998; Hewitt, Shelton, & Esch, 1999; Murillas, Martin, Ramos, & Portero, 1999; Penzak, Chuck, & Stajich, 2000; Thomas et al., 2000). These two classes of drugs work by different mechanisms and may have synergistic activity. Multiple adverse interactions between these classes of drugs and PIs have been noted, particularly in relation to their effects on the cytochrome (CY) P450 system (Meienberg et al., 2001; Penzak & Chuck, 2000).

Insulin-sensitizing agents have been less studied within the context of LDS. Treatment with metformin has produced significant improvement in insulin sensitivity and decreases in central adiposity and other cardiovascular risk markers (Hadigan, Corcoran, Basgoz, et al., 2000; Hadigan, Rabe, & Grinspoon, 2002; Saint-Marc & Touraine, 1999). Thiazolidinediones may be of use for increasing insulin sensitivity and subcutaneous adipogenesis (thus, reversing lipoatrophy) (Gelato et al., 2002; Grinspoon, 2001). However, this class of drugs is also metabolized by various isoforms of CYP450, thus presenting potential adverse drug interactions with PIs.

**Exercise Training**

As an alternative or complement to drug therapies to normalize LDS metabolic changes, endurance (also known as aerobic) exercise training has been shown in several populations outside of people with HIV to be
effective in lowering total and LDL cholesterol and triglyceride levels, and raising HDL cholesterol (Buemann & Tremblay, 1996; Durstine et al., 2001; Halbert, Silagy, Finucane, Withers, & Hamdorf, 1999; Tran, Weltman, Glass, & Mood, 1983). Likewise, endurance and resistance training (weight lifting) has been shown to enhance insulin sensitivity and glucose tolerance (Buemann & Tremblay, 1996; Ivy, 1997). Less clear is the association between exercise and visceral adiposity, but data in one study (Schwartz et al., 1991) revealed a preferential reduction in abdominal adiposity with exercise and other investigators have suggested that the positive metabolic effects of exercise may be mediated in part through weight loss (Buemann & Tremblay, 1996; Durstine et al., 2001). Thus, exercise reduces known anthropomorphic and metabolic risk factors for CAD and has the potential to do so in LDS.

Aerobic and endurance exercise training have been shown to be safe for individuals with HIV disease (Nixon, O’Brien, Glazier, & Wilkins, 2001; Smith et al., 2001; Terry, Sprinz, & Ribeiro, 1999), producing no increase in plasma viremia (Roubenoff, Skolnik, et al., 1999) or further immune compromise (Nixon et al., 2001). Additionally, exercise produces consistent enhancements in psychological well-being in HIV-infected samples, with some limited evidence for a positive impact on circulating CD4+ lymphocytes (Nixon et al., 2001). However, exercise as a primary or adjunctive treatment for the anthropomorphic and metabolic abnormalities associated with LDS has been sparsely studied.

In LDS, combined endurance and resistance training showed a decrease in overall body adiposity in general (Jones, Doran, Leatt, Maher, & Pirmohamed, 2001; Roubenoff, Weiss, et al., 1999) and central adiposity specifically (Roubenoff, Weiss, et al., 1999). Resistance training alone showed little or no effect on central adiposity in LDS or healthy individuals (Treuth et al., 1994; Yarasheski et al., 2001). Roubenoff, Weiss, et al. (1999), in a small pilot study of 10 men who self-reported central fat accumulation, found that 16 weeks of combined training (20 minutes of aerobic activity, 1 hour of high-intensity lifting to work all major muscle groups, 3 days/week) significantly reduced trunk fat. This study enrolled participants with a wide range of age, CD4+ lymphocyte numbers, and viral loads, making risk for central adiposity and potential response to training highly variable. Likewise, Jones et al. (2001) (n = 6 men) found that 10 weeks of combined aerobic and resistance training (similar to that of Roubenoff, Weiss, et al., 1999) produced a significant decrease in total body fat with an increase in total body mass; however, no regional mass changes were reported. Functional capacity (i.e., strength) and cardiopulmonary fitness were increased in these studies.

Changes in LDS-related dyslipidemia have also been reported with exercise. In 18 HAART-treated men, Yarasheski et al. (2001) found that 16 weeks of progressive weight lifting (three upper and three lower body exercises done for 1 to 1.5 hours/day, 4 days/week) reduced serum triglyceride levels without reducing whole body or regional adiposity. There were no changes in cholesterol, insulin, or proinsulin levels; however, levels of these were not as high at the beginning as were the triglyceride levels. The investigators hypothesized that the increase in lean tissue was responsible for increasing the clearance of triglycerides from the circulation. Another small study (Jones et al., 2001) found that combined endurance and resistance training significantly reduced total cholesterol and triglycerides levels in a male sample with LDS.

Whole body insulin resistance is believed to be mostly due to impairments of glucose transport in peripheral insulin-sensitive tissue, especially skeletal muscle (Buemann & Tremblay, 1996). Aerobic capacity and capillary density of skeletal muscle have been positively associated with whole-body insulin sensitivity (Buemann & Tremblay, 1996). Aerobic capacity of skeletal muscle mitochondria was also positively correlated with insulin sensitivity (Simoneau, Colberg, Thaete, & Kelley, 1995); therefore, muscle fibers with high aerobic capacity may be the most insulin-sensitive. Endurance exercise efficiently increases the oxidative profile of muscle fibers (Bassett, 1994), and resistance training increases muscle mass, so both types of training (or a combination) have the potential to result in increased insulin sensitivity (Yki-Jarvinen & Koivisto, 1983). Studies in individuals other than ones with HIV have shown a positive association between habitual physical activity and insulin sensitivity (Feskens, Loeber, & Kromhout, 1994; Regensteiner et al., 1991). Studies relating maximal oxygen uptake (VO2max), to glucose utilization have demonstrated a positive correlation between

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insulin sensitivity and aerobic power independent of age and relative body weight (Endre, Mattiasson, Hulthen, Lindgarde, & Berglund, 1994; Rosenthal, Haskell, Solomon, Widstrom, & Reaven, 1983). Additionally, intervention studies have shown that mild to moderate endurance training can improve insulin sensitivity (Hurley et al., 1984; Jennings et al., 1986; Oshida, Yamanouchi, Hayamizu, & Sato, 1989; Seals, Hagberg, Hurley, Ehsani, & Holloszy, 1984). Resistance training alone has also demonstrated the capacity to enhance insulin sensitivity (Craig, Everhart, & Brown, 1989; J. P. Miller et al., 1994; W. J. Miller, Sherman, & Ivy, 1984), and when endurance and resistance training are compared, a similar training-induced glucose tolerance has been observed (Smutok et al., 1993; Smutok et al., 1994). No studies have looked at the effect of exercise on insulin sensitivity or insulin levels in LDS.

Although incomplete, evidence is suggestive that exercise training may ameliorate components of LDS. The few studies to date are particularly limited by lack of control group comparisons and small sample sizes that produce insufficient power to test the hypotheses. Furthermore, broad inclusion criteria have allowed wide variance in disease stage and duration of HAART. As well, lack of control for confounding variables (i.e., smoking, age, diet, family history) further limits the interpretation of the results as a whole. Although the optimal exercise prescription to treat anthropomorphic and metabolic abnormalities associated with HIV LDS is not known, it is evident that some changes begin to appear within the time frame of these exercise studies (around 3 months), suggesting the need for longitudinal studies to examine further changes that may occur with long-term adherence.

Facial Augmentation

LDS-related facial lipoatrophy appears to be irreversible (James, Carruthers, & Carruthers, 2002). Thus, augmentation with various substances in the nasolabial and buccal regions is emerging as an option for some individuals. Clinical trials of facial augmentation have not been conducted in LDS; however, a recent review of facial implant strategies (James et al., 2002) has suggested their usefulness in LDS. In brief, collagen (Klein & Rish, 1985; Pollack, 1990), cadaver fascia or dermis (Burres, 2001; Shore, 1999), and autologous fat may be used to improve appearance of facial lipoatrophy, but none are permanent and they are expensive given their limited durability. Given the irreversibility of facial lipoatrophy, James et al. (2002) suggested that synthetic permanent augmenting agents (i.e., silicone, GoreTecx) hold the most promise in LDS.

Liposuction

Some individuals with disfiguring lipohypertrophy of the abdominal and dorsocervical regions have suction-assisted lipectomy (or liposuction) to normalize appearance. Three published case reports (Chastain, Chastain, & Coleman, 2001; Ponce-de-Leon, Iglesias, Ceballos, & Ostrosky-Zeichner, 1999; Wolfert, Cetrulo, & Nevarre, 1999) indicate esthetically pleasing results, high patient satisfaction with results, and no complications. However, the permanence of these results is unknown and metabolic abnormalities are unlikely to be affected. Furthermore, because abdominal lipohypertrophy is primarily in the visceral depot, liposuction may not produce the desired effects in the most severe cases. As with any surgical procedure, infection is a risk in an immunocompromised host, but most individuals opting for liposuction would be immunologically stable given HAART. Also, given that liposuction is considered a “cosmetic” procedure, in most cases, insurance reimbursement may be difficult.

Hormonal Therapy

A few studies have investigated the effect of various exogenous hormones on the components of LDS. Decreased growth hormone (GH) levels have been found in individuals with LDS relative to HIV-infected individuals without LDS and normal controls (Rietschel et al., 2001). Furthermore, increased levels of visceral abdominal fat predicated low GH levels (Rietschel et al., 2001). Administration of recombinant human growth hormone (rhGH) is a potential treatment for excess visceral fat. A small one-group prospective study of 10 participants with LDS fat redistribution that received 6 mg of rhGH every day for 3 months found a decreased hip-to-waist ratio and an increased mid-thigh circumference (Wanke,
Gerrior, Kantaros, Coakley, & Albrecht, 1999). Another small study ($n = 6$) found decreases in trunk adiposity with only 3 mg/day of rhGH over 6 months (Lo et al., 2001). Similarly, a 6-month prospective trial of rhGH in individuals with LDS ($n = 30$) found significant reductions in visceral fat (42% with 6 mg and 15% with 4 mg, every other day dosing), with return to previous levels following drug discontinuation (Engelson et al., 2002). Effects on lipids were inconsistent. Total cholesterol levels fell on the higher dose only, whereas HDL-cholesterol levels increased on the lower dose only, and there was no effect on triglyceride levels. Insulin sensitivity actually fell, and 4 patients developed frank diabetes. Lo et al. (2001) also found that rhGH produced initial decreases in insulin sensitivity, but glucose tolerance returned to baseline by 6 months of therapy. Significant myalgia was common in all studies. Given its high cost, the need for long-term therapy, and troubling side effects (especially related to glucose tolerance), the use of rhGH warrants further study for use in LDS.

Anabolic steroids have been suggested as a means to normalize the appearance of individuals with LDS by increasing lean body mass on limbs with lipoatrophy (Gold & Batterham, 1999). However, there is little evidence that anabolic steroids can affect the metabolic and fat redistribution abnormalities associated with LDS (O’Mahony, Price, & Nelson, 1998). Actually, anabolic steroids have been shown to increase lipid levels and insulin resistance (Glazer, 1991), so their use in LDS is cautioned. However, a small pilot study ($n = 11$) found that treatment with nandrolone decanoate (100 mg/week) did not worsen lipid or insulin levels and resulted in increased weight and lean body mass (Gold & Batterham, 1999). The changes in body composition were viewed as favorable by individuals who felt the increases in arm and leg size contributed to a more “balanced body image” regardless of the composition of the change (Gold & Batterham, 1999). Given its potential metabolic side effects, it is doubtful that anabolic steroids will play a major role in the management of LDS.

Low levels of the adipocyte hormone leptin have been found in individuals with LDS who have a predominant phenotype of lipoatrophy (Estrada et al., 2002). Leptin is an important regulator of energy homeostasis and fat storage (Rosenbaum & Leibel, 1999). Thus, supplementation with leptin may ameliorate metabolic abnormalities associated with LDS in individuals who are leptin deficient. A recent study found that daily injections of recombinant leptin administered for 4 months at escalating doses to 9 women with LDS and low leptin levels resulted in significant decreases in triglyceride levels and insulin resistance. The role of leptin in human physiology is not yet completely understood as it is a relatively recently discovered hormone. The results of this study are intriguing and require replication in a large sample. Not all individuals with LDS have low levels of leptin (Estrada et al., 2002), so its usefulness may be limited.

Nursing and LDS

Nurses can play a crucial role in the management of LDS. Gaining knowledge related to LDS is important, so nurses can educate patients to make informed decisions regarding treatment. But like many issues related to HIV disease, there still appears to be more questions than definitive answers. In particular, patients may be concerned about particular antiretroviral agents that may be more heavily implicated in the development of LDS than others. Indeed, ritonavir appears to have a robust adverse effect on triglyceride levels (Periard et al., 1999; Sullivan, Feher, Nelson, & Gazzard, 1998; Sullivan & Nelson, 1997; Thiebaut et al., 2000), whereas stavudine is consistently linked to lipoatrophy (Mauss et al., 2002; Saint-Marc et al., 1999; Saves et al., 2002; van der Valk et al., 2001), but patients need to be aware that these agents are not the confirmed “smoking guns” and that avoiding them does not mean they will avoid LDS.

Monitoring of LDS requires laboratory tests with which some HIV patients will be unfamiliar. In addition to teaching the interpretation and significance of CD4+ lymphocyte numbers and viral loads, nurses caring for patients with LDS should be teaching about lipid profiles, glucose monitoring, and techniques such as dual-energy x-ray absorptiometry (DXA) and abdominal CT scans, which are increasingly being used to assess body composition. The National Cholesterol Education Program (Expert Panel on Detection, Education, & Treatment of High Blood Cholesterol in Adults, 2001) has developed a thorough review...
of lipid profiles. Likewise, Schwenk (2002) provides a comprehensive overview of body composition assessment within LDS. In addition, the International AIDS Society–USA Panel recently published recommendations for the assessment and treatment of metabolic complications associated with HAART (Schambelan et al., 2002). These referenced guidelines provide important information that can be useful for patient teaching.

Healthy lifestyle choices that may decrease the cardiovascular risk of LDS can be promoted in patients. Smoking may play a role in worsening dyslipidemia, and it is clearly a risk factor for cardiovascular disease (Keil, 2000). Assisting patients with smoking cessation programs is warranted. Diet modification (restriction of total fat to 25%-35% and saturated fat to < 7% of daily caloric intake, and cholesterol to 200 mg/day) is the first-line treatment for dyslipidemia in the general population (Expert Panel on Detection, Education, & Treatment of High Blood Cholesterol in Adults, 2001). In the absence of results from randomized, controlled clinical trials evaluating specific dietary interventions in patients with LDS, it is prudent to recommend these dietary modifications (Schambelan et al., 2002). Exercise, as discussed previously, shows promise as an effective adjunctive treatment for LDS. Nurses can help patients set realistic exercise goals. Given the cardiovascular risk factors associated with LDS, patients may be at a high risk for adverse cardiovascular events during exercise (American College of Sports Medicine & Roitman, 2001). For this reason, all patients with LDS should be assessed by their primary health care provider using the safety guidelines of the American College of Sports Medicine (American College of Sports Medicine & Roitman, 2001) before they begin an exercise program.

Nurses must be aware of the psychosocial impact of LDS and intervene accordingly. LDS can lead to depression, stigma, and body image disturbances. Nurses should assess for these regularly and assist patients to develop adaptive coping mechanisms. Nurses should also be aware that fear of LDS (or worsening of the syndrome) may play a role in medication adherence. When assessing reasons for nonadherence, nurses should investigate the role LDS may play.

References


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