HIV-Associated Lipodystrophy

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The metabolic abnormalities associated with HIV and highly active antiretroviral therapy (HAART) pose an increasing concern among patients and HIV providers as patients live longer. The lipodystrophy syndrome, known as HIV-associated Adipose Redistribution Syndrome (HARS), has been most distressing for patients, as they can feel disfigured by the significant alterations in appearance. Lipodystrophy may occur with or without lipid abnormalities, and treatment of lipid disorders has not typically helped the changes in body morphology.

Lipodystrophy is divided into two main categories: fat accumulation and fat wasting, the latter known as lipoatrophy. These may occur together in the same patient, or may occur independently. The fat redistribution syndrome results in fat accumulation in the neck, breast, chest and abdomen while the fat loss occurs most strikingly in the limbs, buttocks and face.

The etiology of the fat maldistribution syndromes remains unknown. The lack of standardized definitions and of practical ways to measure fat loss/gain have further hampered progress, and led to an under-appreciation of the problem. It seems that the more you look, the more you find. Protease inhibitors were first indicted as the culprit, with coinage of the term "protease paunch." However, fatty changes also occurred in patients only on reverse transcriptase inhibitors and even occasionally in patients who had never taken antiretrovirals.

Attention then shifted to the nucleoside reverse transcriptase inhibitors (NRTIs). Similarity of lipodystrophy to non-HIV associated hereditary diseases of mitochondrial dysfunction led researchers to consider mechanisms of mitochondrial toxicity, possibly related to the NRTIs. Mitochondrial toxicity may well play a role in lactic acidosis and peripheral neuropathy, for example, but has been less clearly linked to lipodystrophy. The cytokine tumor necrosis factor alpha (TNF-alpha) has been implicated as having a role in lipodystrophy. In addition, factors of older age, white race, lower nadir CD4+ cell count, and immune reconstitution have been associated with changes in fat deposition.[1] Thus, lipodystrophy is likely multifactorial in its origins and more research continues in this arena.

Even more distressing has been the lack of effective therapies for the lipodystrophy syndrome. Strategies have included antiretroviral switches, therapy interruptions, and various pharmacological interventions. Some of the more successful therapies have been anabolic steroids and growth hormone, often with testosterone supplementation.

In term of switch strategies, interest initially focused on switching patients off protease inhibitors while maintaining full viral suppression. Studies looking at switches to efavirenz, nevirapine, and abacavir have been presented, and success in maintaining viral suppression can depend on which therapy is chosen.[2] Some of the best data has accumulated with efavirenz, where in one study in the US, 7% of patients who switched to efavirenz had virological breakthrough,

compared to 15% of those staying on their protease inhibitor.[3] Improved adherence is suspected of playing a role here. No consistent reversal of lipid changes or fat maldistribution has been demonstrated in multiple trials.

Evidence suggesting a role of NRTIs, especially stavudine, in lipoatrophy has come out of several cohort studies. In an Australian trial, 111 men with lipoatrophy who were on a thymidine analog (77% stavudine, 23% zidovudine) were randomized to switch to abacavir or continue their current regimen.[4] There was a statistically significant increase in limb fat as measured by DEXA and confirmed by CT scan in arm, thigh, and abdominal fat. However, these changes were not clinically perceptible to the patients or their physicians. Non-thymidine NRTIs may be associated with fewer metabolic toxicities, and ongoing strategies include utilizing these as nucleoside backbones in naïve patients, to see if lipodystrophy may be avoided.

Therapies for lipodystrophy have been largely disappointing. Strategies to date have included both medical and cosmetic interventions. Rosiglitazone, a thiazolidinedione, has been studied, as it decreases insulin resistance in diabetics, while promoting an increase in subcutaneous fat. Studies in HIV-infected patients have yielded conflicting results. A double-blind, placebo-controlled study of rosiglitazone in 108 men with lipoatrophy was presented at the 11th Conference on Retroviruses and Opportunistic Infections in February, 2004 by Andrew Carr of Australia.[5] While insulin sensitivity improved, lipoatrophy did not over the 48 weeks of the study.

Recombinant growth hormone is the other therapy that has been studied intensely, and it does appear to work in decreasing visceral fat. When used in traditional HIV wasting, injectable recombinant human growth hormone (r-hGH) increases lean body mass and decreases body fat. In a large trial reported at the 14th International Conference on AIDS in Barcelona , Spain in 2002, there was a significant decrease in visceral fat content when 4 mg/day subcutaneously was injected , and a trend toward significance with 4 mg every other day.[6] In a study of 757 patients, 646 of whom completed 12 weeks of therapy, patients were randomized to receive recombinant growth hormone at 6 mg/day, 6 mg every other day, or placebo.[7] Body weight and lean body mass increased significantly over placebo, with a greater decrease in truncal fat than limb fat. In a dose-finding trial of low-dose, maintenance recombinant human growth hormone, previously treated patients were randomized to receive either 1 mg or 2 mg of daily r-hGH for an additional 24 weeks.[8] Even at 1 mg, reductions in truncal fat were maintained. The cost of this therapy, however, makes it an impractical option for many of our patients.

Measurement of testosterone is recommended by many HIV experts, whenever wasting or significant lipodystrophy is encountered. Generally the unbound, or free, testosterone is the test of choice for HIV-infected individuals. Replacement therapy with topical patches, gels, or mucocutaneous tablets is preferred over intramuscular injections, as these give a more physiologic, therapeutic drug level, as opposed to the high peaks and low troughs associated with the injectabe forms of testosterone.
Increasingly patients have turned to plastic surgeons for assistance with some of the head and neck lipodystrophy problems, though often having to pay out-of-pocket. Buffalo humps can be

successfully treated with liposuction, though the recurrence rate is high. For moderate to severe facial lipoatrophy, injections of collagen, polylactic acid compounds, and other materials have produced some improvements for patients, but the length of benefit appears to vary with the type of compound utilized. Individual treatments can be as much as $600.00, and often 5-6 treatments are required.

Clearly, we need a better understanding of the causes of lipodystrophy, and better treatment options for our patients. Perhaps some of the newer antiretroviral therapies will have fewer of these types of side effects when utilized in treatment-naïve patients. It remains to be seen whether avoidance of known mitochondrial toxins, particulary the thymidine anaologs, in initial HAART regimens might decrease the incidence of lipoatrophy.

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