Miller reports the results of a 3-month program of progressive resistance and aerobic exercise training in 2 perinatally HIV-infected girls: a normal-weight 10-year-old and an overweight 17-year-old. By the end of the program, both had decreases in body mass index (BMI); lost fat, including visceral fat, by at least some measures; and gained significant muscle strength. One had improved cardiovascular fitness, and both showed further improvements after completing a home-based program after the initial 12-week program.

While neither of these patients had signs of body shape changes or metabolic abnormalities commonly associated with lipodystrophy, the author suggests that exercise might prevent the onset of these problems. As in adults, alterations in body fat distribution, insulin sensitivity, and dyslipidemia have been documented in HIV-infected children and adolescents; these effects are primarily associated with the use of antiretroviral therapy. While the physical changes achieved in the 2 cases reported here may benefit HIV-infected adolescents in general, they would be valuable especially in those with lipodystrophy.

The prevention and the treatment of these abnormalities by nondrug means are particularly important areas for research in children. Longer duration of HIV therapy has been associated with the onset of lipodystrophy; children begin antiretroviral therapy early in life and face a lifetime of exposure, which carries with it the risk of premature cardiovascular disease. While newer medications may avoid some of these problems, treatment options are fewer in children than in adults because of the limited availability of pediatric formulations.

Despite its limitations, this case study presents an opportunity to review the status of this very important and largely overlooked field of clinical research. Arpadi first reported a case of fat distribution alterations in an HIV-infected 9-year-old in 1992 and in 2001 published the results of a longitudinal study of body composition changes in 28 HIV-infected children with and without lipodystrophy. Lipodystrophy was associated with protease inhibitor (PI) and stavudine use as well as with a high HIV RNA level and low CD4 count at baseline. The same year, Brambilla and associates published the results of a study of 34 HIV-infected children who were receiving PI-containing regimens and who were pair-matched with uninfected children for age, sex, and BMI. Dual-energy x-ray absorptiometry showed peripheral fat loss in all HIV-positive children, even in the group without clinically apparent lipodystrophy. However, increased intra-abdominal fat deposition as shown by whole-body MRI was found only in the HIV-infected children with clinical signs of lipodystrophy.

Metabolic changes in HIV-infected children have also been described. Bitnun and coworkers reported that children treated with a PI-containing regimen (n = 30) had significantly higher total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels than PI-naive children (n = 20). When Lainka and associates compared children receiving NRTI-based therapies with others receiving combination therapy containing PIs, the children receiving PIs had significantly higher blood concentrations of total cholesterol, LDL cholesterol, and triglycerides in both the fed and fasting states. The European Pediatric Lipodystrophy Group performed studies in 280 HIV-infected children, one of the larger published reports to date, and encountered prevalences of hypercholesterolemia and hypertriglyceridemia of 27% and 21%, respectively; 38% had elevation of either cholesterol or triglycerides, while 10% had elevation of both. Disorders of glucose metabolism...
were revealed by frequently sampled intravenous glucose tolerance tests performed by Bitnun and colleagues\(^8\): in a group of 33 prepubescent (mean age, 9 years) HIV-positive children receiving PI-based regimens, insulin sensitivity was reduced and beta cell response to that insensitivity was impaired compared with 15 HIV-positive PI-naive children of similar age.

While these and other observations clearly demonstrate a substantial risk of lipodystrophy and related conditions among HIV-infected children and adolescents, there is little progress to report with respect to treatment. In contrast, a variety of approaches have been evaluated in HIV-infected adults with fat distribution and metabolic abnormalities.\(^14\) Switching medications, especially from a PI-based regimen to an NNRTI-based regimen, has been shown to improve the metabolic profile. Also, there has been some restoration of peripheral subcutaneous fat with the discontinuation of thymidine NRTIs. In the Mitochondrial Toxicity (MITOX) trial, there was an average 35\% increase in limb fat 128 weeks after switching from zidovudine to abacavir.\(^15\) There is also preliminary evidence that oral supplementation with uridine can promote fat gain.\(^16\) No change in antiretroviral treatment has been shown to significantly reduce excess visceral fat. Visceral fat was reduced an average of 42\% in a study evaluating the use of recombinant human growth hormone\(^17\); however, at doses that minimize adverse effects, the reduction averaged only 19\% after 12 weeks,\(^16,19\) and any beneficial effect was reversed after discontinuation of therapy.

Other medications that have been applied experimentally or clinically to treat important features of lipodystrophy in adults include metformin and rosiglitazone for managing insulin resistance and statins for dyslipidemia. In addition, some improvement has been seen in fat distribution, although results differ across studies. Many studies have investigated plastic surgery for the treatment of subcutaneous lipoatrophy. Weight loss by diet and/or exercise has also been attempted, with improvements in visceral fat and, in one case, in lipid profile.\(^20,21\)

In contrast, there is but a single reported study of the treatment of lipodystrophy in children. In the First Pediatric Switch Study, the PI in the current regimens of 17 children (aged 2 to 13 years) was replaced with the NNRTI efavirenz while the dual NRTI backbone was unchanged.\(^22\) After 48 weeks, there were significant decreases in serum total cholesterol, triglyceride, and LDL cholesterol levels. No changes in glucose or insulin levels were noted. Although body fat content did not change, lean body mass significantly increased. Whether this observed effect reflected normal growth in these children or an improvement in body composition is not clear. While this well-designed trial offers encouraging data about how to address the metabolic consequences related to antiretroviral therapy in children while still maintaining viral control, the body composition results are ambiguous and the effect is limited to patients who have NNRTI-sensitive HIV virus.

Thus, the role in children for interventions tested in adults is unknown, and many of those therapies involve the risk of short- and long-term adverse effects. While lipoatrophy may be best prevented or treated through the avoidance of thymidine analogues, the prevention of many cardiovascular disease risk factors, including obesity, accumulation of visceral fat, dyslipidemia, and impaired insulin sensitivity, may be possible with nondrug alternatives. In HIV-negative children, many studies have shown that diet and exercise are effective interventions for obesity.\(^23-25\) Investigations of the safety and efficacy of exercise programs in HIV-positive children are of potential clinical importance, and to our knowledge, this report is the first such effort. However, as the author correctly notes, this is a case presentation with only 2 patients, so few conclusions can be drawn.

This report underlines the paucity of data on this topic and the critical need for additional research. At the same time, researchers in this field must take into account the normal growth patterns of children, the changes in lipid and glucose metabolism associated with developmental stages, the limited availability of body composition norms for children and adolescents, and the continuing uncertainty—even in adults—of what exactly constitutes lipodystrophy.

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