Lipodystrophy

Possible therapies for body changes and blood fat and blood sugar problems

Final answers are not yet in on the possible causes of lipodystrophy. It is a puzzling syndrome seen in too many people in the HAART era in which fat may be lost from the arms, legs, buttocks and face and/or gained around the abdomen, above the shoulders, in fatty lumps called lipomas, and, in many women and some men, in the breasts. Many people also experience blood sugar and blood fat abnormalities that many researchers fear may ultimately lead to diabetes and/or heart disease. For now, it appears likely that this is a multifactorial problem that antiretrovirals contribute to, either directly or indirectly or both. Among the research notes on possible causes that I have found interesting are the following:

G Dutch researchers have reported that nucleoside analogues (drugs like AZT) may cause mitochondrial toxicity (mitochondria are the energy factories inside cells) that could account for at least some of the lipodystrophy problems, including lactic acidosis, as well as other drug side effects, including neuropathy (nerve pain and numbness) and myopathy (muscle pain).

G Many reports from recent conferences indicate that there may be specific effects of individual drugs that may contribute to elevated blood fats and fat maldistribution and blood sugar problems.

G The cytochrome p450 (CYP) enzymes are put under stress by many drugs, including both over-the-counter and prescription drugs used by many prior to HAART. This stress can result in either inhibition or induction of these enzymes. The conversion of cholesterol into cortisol and testosterone is dependent on CYP enzymes and may have been adversely affected by this stress, resulting in somewhat increased cortisol (due to induction of certain CYP enzymes, probably CYP11) and decreased testosterone (due to inhibition of other CYP enzymes, probably CYP17). These abnormal hormone levels have been widely reported in people living with HIV, both before and after HAART.

HAART, in general, and protease inhibitors in particular put additional stress on the CYP enzymes, both in the gut and the liver. Of those so far studied, it is known that all the protease inhibitors put particular stress on the CYP3A4 enzymes. Some of these drugs are also known to stress the CYP2C9, CYP2C19, and CYP2D6 enzymes, and may also stress the higher numbered enzymes. This may worsen the overproduction of cortisol (although not, perhaps, to a detectable level, at least initially) and cause a resulting increase in insulin insensitivity. The combination of too much cortisol with too little testosterone would be synergistic in creating insulin insensitivity.

German researchers have reported (*AIDS* 12:F167-F173, 1998) that patients who receive protease inhibitors are at significant risk of developing peripheral insulin resistance. Dr. Ravi Walli of Ludwig-Maximilians Universitat Munchen and colleagues evaluated the effects of PIs on insulin sensitivity in 67 HIV-positive patients and found that those on indinavir, saquinavir, or nelfinavir had significantly decreased insulin sensitivity. "All treated patients with impaired (n=4) or diabetic (n=9) oral glucose tolerance, and 4 out of 11 patients with normal glucose tolerance showed peripheral insulin resistance." All 67 treated patients also experienced significant increases in total triglycerides and cholesterol. There were no significant differences associated with use of any of the three PIs. "The most striking finding of this study was the significantly lower insulin sensitivity in the patients treated with protease inhibitors compared with therapy-naive patients," they say.

G Testosterone deficiency, common in HIV positive men and women, is known to cause insulin resistance

in men. Although this is less clear in women, the lack of testosterone could increase the likelihood that women's bodies would lean toward building fat rather than muscle tissue.

G A deficiency of glutathione and other thiol compounds, known to exist from the earliest days of HIV infection, takes away the glutathione that is one of the three building blocks of the glucose tolerance factor (GTF), a compound that also includes chromium and the B vitamin niacinamide. GTF is required for the maintenance of cells' sensitivity to insulin. In addition, both insulin and its receptors contain thiols. Changes in the availability of these compounds could alter the binding of insulin to its receptors in a way that makes it less useful, contributing to insulin insensitivity.

G As well, the demands on the liver to detoxify these drugs further depletes the thiol compounds and decreases the liver's ability to function properly. Since the liver is the main regulator of blood fats and a crucial stabilizer of blood sugar, the havoc being wreaked there might well at least partially account for the elevated triglycerides and increased blood sugar that many are experiencing along with the fat changes.

G The places in the body that have the greatest blood supply tend to have the greatest formation of fat. This includes the area around the gut as well as behind the neck and in the pelvis. With normal functioning, glucose should be delivered to cells and, with the assistance of insulin, transported inside the cells to be used for energy or, when there is excess, converted to fat. When this doesn't happen due to insulin insensitivity, more insulin is produced by the body, leading to the high insulin levels seen in people with lipodystrophy.

Unfortunately, with insulin insensitivity this won't solve the problem of the excess glucose. Since the liver has to get rid of it somehow, it will then begin converting the glucose into triglycerides. The closest location with the largest blood supply where the liver can then dump those triglycerides is in the gut and the pelvic area. A secondary possibility is the area behind the neck, also rich in blood supply.

In contrast, peripheral areas of the body—the arms, legs and face—have poorer blood supply. In addition, the supply of insulin to those areas may be insufficient to counter the insulin resistance. Therefore, energy transfer there would be inadequate. Ultimately, the rate of breakdown of fat would then exceed the formation of fat, resulting in the loss of fatty tissue. Yep, that means skinny arms and legs and a gaunt face.

There are many other theories as to causation, and for now it seems that the more researchers ponder the problem, the more complex it becomes. But while researchers ponder complicated theories on the possible mechanisms via which the drugs might contribute to the problem, it is important for anyone living with HIV to be aware of the possible approaches to therapy that may be important, both to reshape the body, and to prevent long-term complications from liver disease, heart disease and/or diabetes.

Possible Therapies

The use of therapies aimed at reshaping the body—including human growth hormone for reducing abnormal fat accumulation, and facial reconstruction via the use of polylactic acid injections—and preventing heart disease, liver disease, and blood sugar problems may be very important for anyone trying to live *well* with HIV, not just longer.

G Human growth hormone

On the pharmaceutical front, it's been reported that recombinant human growth hormone (Serostim) has at least partially reversed the accumulation of fat in both the abdominal area and the area behind the neck (the Buffalo hump problem). In some people, it has also reduced or eliminated lipomas. There have been some reports on reductions of elevated triglyceride levels but there is conflicting evidence on this, with other

reports of no improvements in either triglyceride or cholesterol levels. Although there have also been some reports of restoration of lost tissue in the arms and legs, the likelihood that growth hormone will stimulate fat burning makes most think that it is not advisable for anyone with lipodystrophy that involves fat wasting in the arms, legs, buttocks, or face (as opposed to traditional wasting which involves the loss of muscle tissue; for this, growth hormone is a very effective therapy). Confusingly, however, some people who have a combination of fat accumulation in the belly or over the shoulders, with fat loss in the arms and legs have actually reported that the use of Serostim to reduce the belly or buffalo hump also seemed to result in some improvement in the skinny arms and legs. Why this would work is not clear and the improved look of the limbs might just be a result of fluid accumulation there (a possible side effect of growth hormone) but, in any case, enough people have told me that they are pleased with the combined results that I report it to you here. For those concerned about worsening already wasted limbs, it would probably be best to wait until there are results from the clinical trials now studying the use of growth hormone for lipo-associated fat maldistribution.

There have been many reports at recent conferences of improvements in fat accumulation problems in most of those treated with growth hormone. Improvements are generally seen within a few weeks of beginning therapy. The most commonly seen improvements are reductions in buffalo humps (or their complete elimination), loss of fat around the trunk, especially in the belly, and some (although less impressive) reductions in abnormally increased breast size. In some people, there is also some restoration of tissue in the arms, legs, and buttocks (although not usually a full return to normal). Facial gauntness does not seem to improve. Side effects seen in some people with growth hormone can include increased blood sugar, tissue fullness, swollen joints, and carpal tunnel syndrome.

Although the initial dose used was the 6 mg per day, given via subcutaneous injection, that is approved for traditional AIDS wasting, lower doses are now being studied. Treatment advocates have looked at the possibility of using doses of 2 or 3 mg, either daily or every other day, in an attempt to gain the benefits of growth hormone with less risk of side effects and, of course, less expense. Trials are now ongoing to study such lower doses. There are many anecdotal reports from the community saying that lower doses do, indeed, work. For anyone considering stretching the growth hormone from one vial to cover several days, it is important to know that those doing this are mixing the growth hormone with bacteriostatic water (available from most pharmacies with a prescription from a physician), rather than using the liquid that comes with the growth hormone. When refrigerated, this will apparently maintain the safety of the mixture for up to a week.

Using growth hormone for lipodystrophy may seem, on the surface, to be only symptomatic relief, restoring more normal fat distribution in the body, without actually eliminating the cause of these problems. But note that this is not unimportant. An abnormal level of body fat—and, in particular, abnormal truncal obesity (accumulation of fat around the gut, often called a "beer belly")—has been shown to be a major risk factor for cardiovascular disease, non-insulin dependent diabetes mellitus, and stroke in both men and women. With increasing numbers of reports that a significant percentage of people on HAART are developing both cardiovascular problems and diabetes, it seems particularly important to address every possible risk factor for these diseases. If growth hormone can effectively reduce abnormal fat accumulations, this may be very important for long-term strategies to prevent these complications in people living with HIV.

It may also be very important to improve emotional wellbeing. Abnormal fat accumulation has caused many considerable distress so the body improvements that growth hormone may bring could be very important for some people's psychological health. And last but not least, for many it may help to reduce the discomfort or pain or sleep disorders or digestive problems that abnormal fat accumulation may cause.

G Cosmetic surgery for facial reshaping

The best current hope for reversing the lipodystrophy-associated facial wasting appears to be injections into the wasted areas of the face of a substance called polylactic acid (PLA). It works because the

tiny powdered particles that are injected trigger the body's own production of collagen, a natural protein substance that's a normal part of skin. Since the particles are so small, the development of new collagen looks completely natural. You just end up with a new layer of your own skin. The end result appears to be a much more natural restoration of normal facial appearance than is usually achieved with other approaches that have been tried (cheek implants or injections of filler substances like silicon or fascian or collagen).

The first trial of PLA (in this case, using the French brand called New-Fill) for facial wasting came from Parisian surgeon Patrick Amard, MD. At the 2nd International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV (Toronto, September 13-15, 2000), Amard reported on research in which every two weeks, 26 male HIVers who had developed facial wasting (severe in 20, moderate in five) while on antiretroviral drugs (87 percent on HAART that included a protease inhibitor) were given two injections (a total of 3 cc) into each cheek. The results were, well, uplifting. Assessments based on physical examination and ultrasound of the cheeks showed dramatic increases in skin thickness—up 151 percent by the end of the third month, and a whopping 196 percent after six months. Best of all, 22 of the 26 men reported that their faces were back to normal. Yearlong followup data on these trial participants was presented at the lipodystrophy meeting in Cannes, France, in April, 2001, and showed that the good results were maintained.

Although there's no additional published research to report on the use of PLA for HIV-associated lipodystrophy, it has an impressive track record of successful use in other types of cosmetic surgery—it's long been used in Europe to fill in laugh lines and other wrinkles. It appears to be quite safe, posing no risk of an allergic reaction. And it will gradually disappear over a period of 18 months to two years, a plus if you don't happen to like the results.

Each treatment consists of multiple injections into each cheek, and most people with a moderate amount of fat loss will require at least three repeats, spaced at least three weeks apart, for good results. For those with very severe wasting, a total of up to six go-rounds may be necessary. After that, a booster treatment may be required every year or so in order to maintain the results. Initially, it will take several weeks before changes become visible, but when they do, the HIVers who have tried it sure seem pleased

After POZ's first article on PLA resulted in a deluge of requests for additional information, I interviewed an HIVer, Allen Robinson (not his real name) who had gone to Paris to have Amard do his treatments. Although at the time of the interview he had only had three of the planned six treatments, he concluded by saying, "Before I did this everyone on the beach could pick me out of the crowd. I felt miserable and disfigured. Now my normal face is coming back. I think this is the best approach available."

As to the procedure itself, Robinson says, "The injections are uncomfortable but bearable. The first session was the worst because that's when the surgeon goes the deepest since he's building the base layer that the collagen will develop around. He uses tiny needles but they are jabbed into your face. It's like a dentist who's gone crazy with the novocaine." Although some of the injections seem to hurt worse than others, just depending on the spot that's hit, putting ice on the face before starting and using a topical lidocaine (anesthetic) ointment reduce the pain considerably. And the polylactic acid is actually mixed with lidocaine before it's injected to help prevent pain (150 mg of PLA powder is mixed with 2 ml of sterile water and 1 ml of lidocaine).

It takes about 45 minutes to do the injections in both sides of face. However, there's little if any bruising or pain or swelling afterwards. Ice is applied to the face for 15 minutes after the injections are completed, and then, Robinson says, "You walk out on the street looking fine. Once it's over, it's over. I went out to dinner afterwards, and no one noticed anything."

Although polylactic acid is used in certain dental procedures in the U.S., it is not yet approved for this indication. However, New York City's DAAIR buyers club is importing it via use of the personal importation form. With a prescription from your doc and this form, any US citizen can legally import a personal supply of a drug that is not approved in the US, but is approved in some other country. If US surgeons can be found who are willing to use PLA (see below), it may soon be a therapy available in North America. In the meantime, it is already available in Europe and Mexico.

Because of the considerable interest of so many HIVers in this possible therapy to reverse facial wasting, I personally went to Tijuana, Mexico, to see the procedure done on a half dozen people who agreed to participate in a small trial, and was extremely impressed by the results. The surgeons doing the injections seemed very skilled, in general, and already proficient in this particular procedure. They have been using it for a couple of years for eliminating wrinkles and other cosmetic work in non-HIVers, and are using a modified technique (in essence, the one developed by Patrick Amard, the Parisian surgeon who got the impressive results in the small trial discussed above) for the lipo-associated wasting. I will be returning soon to see the third treatment for the six HIVers participating in this Mexico trial. Three of them had some of the very worst facial wasting I've ever seen so their results should definitely tell the tale. But so far this looks like an amazing success for reversing the facial wasting. The level of discomfort during the injections seemed similar to what Robinson reported, and none of the six people I watched found it unbearable, although there was definitely some pain at times. And yes, indeed, we all went out to dinner that night and had a grand time.

The PLA is far less expensive than other approaches being tried in the US. A San Diego dermatologist went with us to observe and said that she was very impressed by the results, and that the fees shown on the surgeon's list were less than a third what people would pay with most US docs. She also noted that the cost of PLA was staggeringly less than that of substances like collagen. At the clinic in Mexico, the total fee for three visits, including the drug, the surgeon's fees, and the clinic costs, is around $1450 but efforts are underway to reduce that price.

I know that many people would prefer to have their local dermatologist or cosmetic surgeon do the procedure. The problem appears to be the need for specific training in how to do it. After observing the six procedures, I can tell you that it was clear to me that you would need someone very experienced in aesthetic facial procedures, in general, and specifically trained in the use of the polylactic acid substance. It is apparently difficult to inject because of thickness, etc., and it requires insertion in precise places to achieve the desired effect. Unlike collagen or other implanted substances, this is not a case of just sticking in a filler material where you can immediately see the results. Instead, you're getting injections of the PLA that will, over the course of several weeks, prompt your own body to produce collagen in those locations.

It's that locally produced collagen that will actually create the change. Thus, the end result depends on the surgeon being able to predict the likely results if X amount is injected in Y location, and how to fine tune the injections accordingly. I know that while I was watching the procedures I thought to myself "Gee, I wouldn't want to be first in line for this."

Although I am very hopeful that we can get US dermatologists and cosmetic surgeons interested in receiving training to do this procedure (which is being offered at the Mexican clinics for any doc who is interested), I am concerned about surgeons or dermatologists who have NOT been specifically trained in the use of PLA just attempting it on their own. When I was researching the article on this that I wrote for POZ Magazine (June 2001), the only negative stories I heard came from people who used a local US doc who had never before used the substance. Obviously, there may be some US docs who already know the techniques but that's definitely a question you'd want to ask.

It appears that for now many people are planning on taking advantage of the expertise of the Mexican surgeons and getting the procedures done there. The surgeons whom I observed doing the procedures have practices in Reynosa, Mexico, and Tijuana, Mexico (the latter of which will be easier for most people since you can fly into San Diego). The clinic where I observed the surgeries was in Tijuana and the surgeons were Jorge Tagle, MD, and Guillermo Hernandez, MD. Both are very experienced in the procedure and have so far gotten great results in people with lipo-associated facial wasting. Dr. Tagle speaks more fluent English and is willing to discuss the procedure with US docs or patients with concerns. If you are interested in setting up an appointment to have the procedures done, do remember that you have to have a minimum of at least three treatments, spaced three weeks apart. So that means three trips to San Diego and three hops across the border (take your passport as technically you need it although they don't seem to usually ask). And again, for those with really severe wasting, additional treatments may be necessary.

To call from the US, the clinic number in Tijuana, Mexico, at the Hospital del Prado is: 011-526-681-3626 (this is the main office #; Irma Montero is his asst. who also speaks fluent English). Feel free to tell them that Lark Lands suggested that you call, and don't forget that Tijuana is Pacific Time zone.

DAAIR, the large buyers club in NYC which sells the polylactic acid product, has a fact sheet with all this and more info available. DAAIR is also putting together a list of docs who are willing to go for a weekend training session in Tijuana. They'd be delighted to add a doc in your area to the list if you know one who might be interested. They will be doing training sessions as requested. If the technique is ever to be widely available, we certainly need US docs who are willing and able to do it so if you know a dermatologist or cosmetic or reconstructive surgeon who might be interested, do forward this information to them. For more information, go to www.new-fill.com or www.daair.org or call DAAIR (888-951-5433).

G *Regular exercise*

Regular workouts that combine the progressive resistance exercise that is known to increase insulin sensitivity with the aerobic exercise that provides cardiovascular benefit are important parts of a long-term health plan, especially for those suffering from any combination of lipodystrophy problems.

G *Testosterone replacement therapy*

When hormone level tests show the need, testosterone replacement therapy would be important both to increase insulin sensitivity and improve the body's ability to build muscle tissue.**

G *Nutrient supplementation*

Consider taking a high-potency multiple that contains the B vitamins, the antioxidant nutrients, and the major and trace minerals (to ensure the presence of the niacinamide needed to create GTF, as well as providing a base level of the vitamin E, vitamin C, vitamin B-6, vitamin B-12, folic acid, magnesium, and other nutrients that may help provide cardiovascular protection).*

Also consider adding extra amounts of certain nutrients that may be needed in larger amounts to ensure glutathione adequacy and cardiovascular protection. Included are: alpha-lipoic acid (200-400 mg, three times per day), N-acetyl-cysteine (NAC; 500-1000 mg, three times per day), vitamin C (1000-2000 mg, three times per day), vitamin E (1200-1600 IU per day), coenzyme Q-10 (30-100 mg, three times per day), and glutamine (2000-5000 mg, three times per day; increased up to 30-40 grams per day in those with serious muscle loss and wasting).*

Kees Brinkman, MD, and his colleagues have reported that nuke-induced mitochondrial dysfunction may be prevented or reversed with the combination of carnitine, riboflavin, coenzyme Q-10, and a broad spectrum of antioxidants (including E, C, NAC, and selenium) so it is probably very important to include these nutrients for anyone taking nucleoside analogues. These researchers have even reported successful treatment of lactic acidosis, a potentially fatal buildup of lactic acid in the bloodstream, with these nutrients given intravenously.

Also possibly useful is a GTF (glucose tolerance factor) formula that includes 200-300 mcg of chromium, taken three times per day; it's best if this supplement also includes vanadium, another mineral that's crucial for blood sugar control; otherwise, the vanadium can be taken separately.*

It may be very important to use L-carnitine in doses of 3000-6000 mg per day; although not yet studied for HAART-induced increases in blood fats, Italian researchers showed in pre-HAART studies that 6 g of carnitine daily was effective in normalizing abnormally elevated triglycerides in HIV+ people; thus, this may contribute to the multifactorial problem of high blood fats. The pharmaceutical version Carnitor (Sigma Tau Pharmaceuticals) is best since some over-the-counter products have been shown to not contain advertised amounts.

Use of fish oil (1-2 capsules, three times per day) may also help to increase insulin sensitivity and decrease triglycerides.*

Use of magnesium (500-1000 mg per day), often deficient in PWAs, may also be very important for glucose metabolism and the health of the heart.*

For liver protection, the herb milk thistle (*Silybum marianum*) which contains the flavanolignanes silybin, silycristin, silydianin, and isosilybin which, as a group, are commonly referred to as silymarin in doses of 1-2 capsules three times per day may also be very helpful. Silymarin has powerful effects as an antioxidant, a protector of the liver, and an agent that may help improve insulin sensitivity. It both protects healthy liver cells from toxic chemicals by promoting healthy cell membranes, and stimulates protein synthesis which promotes new liver cell growth, thus repairing the liver where it is damaged. Specifically, it promotes repair and regeneration of liver cells (hepatocytes) through the anti-inflammatory silymarin flavonoids found in the plant. These flavonoids have specificity for the liver and act in four main ways: (1) they stabilize cell membranes, acting as anti-inflammatories; (2) they stimulate RNA and DNA synthesis, enhancing regeneration; (3) they conserve glutathione peroxidase, the antioxidant enzyme so important to the liver; and (4) they stimulate enzymatic activity in the liver.

G *Dietary improvements*

It could be very important to replace some of the other fats in the diet with increased amounts of monounsaturated fats—olive or canola oil—both to increase insulin sensitivity and promote cardiovascular health. It is also very important to completely eliminate partially hydrogenated fats from the diet, a major risk factor for heart disease. Harvard researchers have found that intake of the trans-fatty acids created when fats are partially hydrogenated is very strongly tied to the risk for heart attacks and have called for federal regulators to "*aim to greatly reduce or eliminate the use of partially hydrogenated vegetable fats*"[1] Partially hydrogenated fats are found in countless foods, including margarine, shortening, most standard breads, crackers, cookies, and other baked goods, many condiments such as mayonnaise, most commercial salad dressings, and some processed meats and snack foods such as potato chips, corn chips, and french fries. It will be crucial to read labels carefully in order to eliminate these unhealthy fats. If it says "partially hydrogenated" anywhere on the label, do not eat that food. Period.*

G *Drugs that increase cellular sensitivity to insulin.*

There are a number of drugs usually prescribed for Type 2 diabetes that help to sensitize the cells to insulin, and thus reduce abnormally elevated blood sugar. Interestingly, there have been reports of at least partial improvements in fat redistribution problems in those given one such drug, metformin, so there may be multiple benefits from the use of such agents. However, there is considerable potential for interaction of these types of drugs with HAART drugs so choices of particular agents must be made very carefully.

And remember: preventing problems is always preferable to trying to fix them after they're extreme. Beginning these nutrient therapies before beginning HAART—or if it's too late for that, before the onset of lipodystrophy symptoms—may help prevent the problems from ever surfacing, or at least decrease their severity. Now stay tuned for the updates on all this as researchers and activists continue to add to our understanding of the mechanisms involved—and the therapies that may help.

*For much more detail on all these nutrients, see Lark Lands' *Positively Well, Chapter Six, Therapeutic Basics for People Living with HIV*. For more detail on dietary fat and the dietary needs of people living with HIV, see *Positively Well, Chapter Three, Nutrition: A Healing Diet*. Both these and a great deal of additional information is available on the World Wide Web at: www.larklands.net.

For more information on the uses of exercise, testosterone, and other anabolic steroids for people living with HIV, see *Treatment with Testosterone* and *Treatment with Anabolic Steroids* by Lark Lands. Also, see the information found on the PoWeR (Program for Wellness Restoration) website at: www.medibolics.com

1. Willett WC and Ascherio A. Trans fatty acids: Are the effects only marginal? *American Journal of Public Health*. 84(5):722-724, 1994.