HIV Protease Inhibitor–Related Lipodystrophy Syndrome

Andrew Carr

HIV Medicine Unit, St. Vincent’s Hospital, Sydney, Australia

Human immunodeficiency virus (HIV) protease inhibitor (PI) therapy is frequently associated with a syndrome increasingly referred to as lipodystrophy syndrome, which is characterized by peripheral lipatrophy, fat accumulation within the abdomen, in the breasts of women, and over the cervical vertebrae (“buffalo hump”), hyperlipidemia, and insulin resistance. In the largest study to date, peripheral lipatrophy (an estimated 0.35-kg fat loss per month overall from the face, limbs, and upper trunk) was observed in association with all licensed PIs after a median 10 months of PI therapy. Diabetes mellitus type II appears to be a related, but less common, adverse effect. The lipodystrophy syndrome may be a result of the inhibition of 2 proteins involved in lipid metabolism that have significant homology to the catalytic site of HIV protease—namely, cytoplasmic retinoic acid binding protein type 1 and low density lipoprotein-receptor–related protein.

Protease inhibitors (PIs) of HIV confer virological, immunologic, and clinical (including survival) benefits [1, 2]. PIs in combination with nucleoside analogue reverse-transcriptase inhibitors (NRTIs) are now recommended as standard-of-care antiretroviral therapy [3, 4]. The potency and sustained effects of combination PI therapy have led to its wide use. There are many toxicities associated with receiving HIV PIs, which include renal calculi with indinavir; nausea, diarrhea, and perioral paraesthesia with ritonavir; and diarrhea with nelfinavir. These generally occur early in therapy, are not usually serious, and resolve rapidly with discontinuation. Excessive bleeding in hemophiliacs, hepatitis, and portal vein thromboses, although potentially serious, are relatively rare [5, 6].

HIV PIs can also cause hyperglycemia, perhaps due to insulin resistance [1, 7, 8]. Insulin resistance correlates closely with abdominal obesity and hypertriglyceridemia and underlies diabetes mellitus type II [9, 10]. HIV PIs can also cause hyperlipidemia [1]. Generalized wasting is a common manifestation of HIV infection and is predominantly loss of muscle mass [11, 12]. Regional fat wasting, however, has been reported neither in patients with HIV infection nor as a consequence of any drug therapy. However, after the introduction of PI therapy, I and others noted patients with peripheral wasting and/or central obesity, although potentially serious, are relatively rare [5, 6].

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Lipodystrophy was defined clinically by a patient’s report of fat wasting in the face, arms, and/or legs, with or without central obesity, and confirmed by physical examination. Patients with weight change but without peripheral fat wasting were not defined as having lipodystrophy.

Lipodystrophy was observed in 74 of 116 patients (64%) who had been receiving a PI for a mean of 13.6 months (range, 1–39 months) but in only 1 HIV-infected patient who was PI-naive (3%; \( \chi^2 \) test, \( P = .0001 \); table 1). Lipodystrophy occurred with equal frequency in all body regions, including the trunk, except the abdomen where patients reported obesity (figure 1). Lipodystrophy was associated with all PIs, and the median time to onset of lipodystrophy was 10 months (figure 2A). Lipodystrophy did not resolve in any patient.

Dual energy X-ray absorptiometry (DEXA) demonstrated that patients who were receiving PIs had comparable body weight and fat free mass but significantly lower fat mass overall and in each body region (except the central abdomen) than did both PI-naive patients and healthy males. It is important to note that HIV-infected PI-naive recipients had total and central fat mass similar to that of healthy males. Assuming that body fat mass in the PI group before PI therapy was similar to that of PI-naive group, the mean loss in body fat was 0.35 kg/month of PI therapy.

Patients with PI-induced lipodystrophy had significantly longer duration of PI therapy than those without lipodystrophy (15.2 and 10.9 months, respectively, \( P = .0001 \)). Lipodystrophy was not more likely in those with a family history of diabetes mellitus. In addition, other clinical variables, particularly CD4+ lymphocyte counts and HIV RNA levels (viral loads) were not independent risk factors for lipodystrophy.
Figure 1. Characteristic physical features of the lipodystrophy syndrome in several patients receiving HIV protease inhibitors. There is fat wasting of (a) the face, (b) the legs, (c) the arms, and (d) the buttocks, and fat accumulation in (e) the abdomen, (f) the breasts, and the dorsocervical fat pad.
Peripheral lipodystrophy has also been described by Viraben et al. [14] as a common complication of indinavir therapy, and Miller et al. [15] showed that the abdominal distension in patients who were receiving indinavir was the result of accumulation of visceral fat, with stable or declining levels of subcutaneous abdominal fat. The results of the study by Miller et al. demonstrated increased intra-abdominal fat, whereas the DEXA-based study did not; this is probably because DEXA is less effective at the L4 vertebral level at measuring intra-abdominal fat. The results of the study by Miller et al. showed that the abdominal distension in patients who were receiving indinavir was the result of accumulation of visceral fat, with stable or declining levels of subcutaneous abdominal fat. The results of the study by Miller et al. demonstrated increased intra-abdominal fat, whereas the DEXA-based study did not; this is probably because DEXA is less effective at the L4 vertebral level at measuring intra-abdominal fat than single-cut CT.

Herry et al. [16] reported breast hypertrophy in a woman receiving indinavir. No other case has been reported; anecdotes suggest that this is a common problem. Lo et al. [17] reported buffalo hump in a small series of 8 HIV-infected patients. However, half of the patients were not receiving PIs; therefore, it is not clear yet what the relationship is between the condition and PI therapy and/or HIV infection per se.

Metabolic Findings

Patients with lipodystrophy also had significantly higher triglyceride, total cholesterol, insulin, and C-peptide levels and greater indices of insulin resistance than those without lipodystrophy (table 2) [13].

Three PI recipients (2%) had worsening (n = 1) or new (n = 2) diabetes mellitus, as determined by fasting blood-glucose values. For the patient who was a long-standing type I diabetic, daily insulin requirements increased by 70%. Of the 2 new diabetics, 1 required insulin for symptomatic hyperglycemia after 4 weeks of indinavir therapy, at which time lipodystrophy was noted. The second had asymptomatic hyperglycemia that did not require therapy 4 weeks after switching from indinavir to ritonavir/saquinavir and had noted increased fat wasting after 9 months of indinavir therapy.

Several other reports have identified diabetes associated with PI therapy [7, 8]. In previously nondiabetic patients, the clinical presentation was usually asymptomatic and nonketotic (i.e., type II diabetes). The above metabolic data confirm the type II pattern with the demonstration of much more common insulin resistance. It is unfortunate that no study has yet performed oral glucose tolerance tests to formally assess the prevalence of diabetes mellitus among patients receiving all forms of therapy.

Diabetes mellitus type II generally results from both insulin resistance and impaired insulin secretion. This may explain why lipodystrophy is common with PI therapy, but hyperglycemia is relatively rare, since most patients may be able to compensate for lipodystrophy-induced insulin resistance by increasing insulin secretion from pancreatic islet cells.

Neither PI use nor lipodystrophy has been associated with
significant differences in liver function, or leptin, testosterone, sex hormone–binding globulin, prolactin, cortisol, C3, or tumor necrosis factor–α levels.

Comparison of Indinavir with Ritonavir/Saquinavir

A comparison of clinical and metabolic parameters showed that both the lipodystrophy and metabolic features of the syndrome were more abnormal in patients who were receiving ritonavir/saquinavir than in those receiving indinavir alone (table 2; figure 2B) [13]. The contrasting effects of ritonavir/saquinavir therapy and indinavir monotherapy might arise because PIs have varying capacities to cause this syndrome or because a single PI has a different capacity to cause it than does a combination of PIs. The relative contributions of ritonavir and saquinavir have not been assessed, although ritonavir monotherapy frequently causes hyperlipidemia [1]. Whether the new formulation of saquinavir with greater bioavailability (~12%) will cause lipodystrophy when used as monotherapy is not known. There are no data that describe the severity of the syndrome in association with nelfinavir.

Diagnosis

It is important to acknowledge that there is no accepted case definition for lipodystrophy syndrome, nor for the clinical features of lipoatrophy or fat accumulation. This may partially explain why some studies have reported marked differences in prevalence. Such a case definition may not only assist in routine diagnosis but also will assist in comparing the effects of various PIs and the effects of a given PI in various patient populations.

Possible Molecular Basis of the Syndrome

HIV PIs have high affinity for the catalytic site of HIV protease and thus might induce this syndrome by binding and inhibiting homologous human protein(s) that are involved in lipid metabolism. A 12–amino acid sequence (aa 19–30) that spans the catalytic region of HIV protease has 63% homology at the protein level with a region incorporating a lipid binding domain in the low density lipoprotein-receptor–related protein (LRP) and 58% with a C-terminal region of the cytoplasmic retinoic acid binding protein type 1 (CRABP-1; figure 3) [18]. CRABP-1 is an ubiquitous protein that binds virtually all intracellular retinoic acid [19, 20]. CRABP-1 effectively presents retinoic acid to cytochrome P450 3A isoforms that catalyze the conversion of retinoic acid to cis-9-retinoic acid (figure 4). cis-9-retinoic acid is, in turn, the sole ligand of the retinoid X receptor (RXR) [21, 22]. RXR functions as a heterodimer with peroxisome proliferator activated receptor type γ (PPAR-γ) in adipocyte nuclei. Ligand binding to RXR or PPAR-γ inhibits adipocyte apoptosis and upregulates adipocyte differentiation and proliferation, with PPAR-γ being more functional in subcutaneous fat than in central fat [23–26]. Agonists of RXR or PPAR-γ improve abnormal insulin sensitivity and hyperlipidemia, both features of the lipodystrophy syndrome [26, 27]. CRABP-1 has up to 19 binding residues for retinoic acid, including residues 119, 121, 131, and 133 (the first 2 lie within the homologous region in figure 3; the latter 2 are immediately adjacent). Residues adjacent to these binding residues (such as amino acids 125 and 126) are vital to the tertiary structure of CRABP-1 and probably to its binding of retinoic acid [28]. HIV PIs may, therefore, bind to this homologous region within CRABP-1 and thus inhibit the binding of retinoic acid to its binding pocket. The resulting reduction of cis-9-retinoic acid production would reduce RXR activity and hence reduce the differentiation and increase the apoptosis of peripheral adipocytes. Both of these circumstances cause hyperlipidemia by reducing triglyceride storage and lipid release into the circulation. Fat necrosis seems unlikely, since the condition is painless [13, 14].

Cytochrome P450 3A is the sole enzyme known to convert retinoic acid to cis-9-retinoic acid. HIV PIs are potent inhibitors of cytochrome P450 3A. Indeed, lipodystrophy was most severe
in those patients who were receiving ritonavir [13], the most potent cytochrome P450 3A inhibitor of the PIs.

LRP is a hepatic receptor that is important for postprandial chylomicron clearance [29, 30]. LRP is also coexpressed on capillary endothelium with lipoprotein lipase (LPL). The LPL-LRP complex cleaves fatty acids from circulating triglycerides, permitting free fatty acid to enter into adipocytes for storage as fat [31]. The GQDDC sequence of the homologous region in LRP is indeed a probable lipid binding domain. PI binding of hepatic and endothelial LRP would, therefore, exacerbate hyperlipidemia.

Central adipocytes (including perhaps those of the dorso-cervical fat pad) are more metabolically active than are peripheral adipocytes [32, 33]. In the presence of impaired peripheral fat storage and hyperlipidemia, central fat accumulation may occur by default. In the presence of estrogen, lipid is also sequestered in the breasts. Another consequence of accumulation may occur by default. In the presence of estrogen, peripheral adipocytes [32, 33]. In the presence of impaired peripheral adipocytes [32, 33]. In the presence of impaired peripheral adipocytes [32, 33].

CRABP-2 has 97% homology with CRABP-1 and is expressed predominantly in epidermis. Other adverse events associated with HIV PI therapy, such as dermatitis, dry lips, and nail dystrophy may, therefore, also be a consequence of inhibited retinoic acid metabolism in the integument. LRP is also the primary clearance receptor for numerous endogenous pro-teases including tissue plasminogen activator, a natural anti-coagulant [31]. Excess bleeding in hemophiliacs who are receiving HIV PIs suggests that PIs do inhibit LRP function, in this case its uptake of tissue plasminogen activator.

There are other possible mechanisms that could conceivably induce this syndrome. Fat accumulation could be a refeeding effect associated with improved appetite in the setting of suppression of HIV replication; this would not explain lipoatrophy, however. It seems less likely that the syndrome is a direct effect of HIV, since this syndrome is being recognized in patients who are receiving potent antiretroviral therapy. Any possible con-

Table 2. Body composition and metabolic parameters in protease inhibitor recipients with or without lipodystrophy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th></th>
<th>Lipodystrophy</th>
<th></th>
<th>Lipodystrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients (n=74)</td>
<td>Indinavir (n=41)</td>
<td>Ritonavir/saquinavir (n=25)</td>
<td>No lipodystrophy (n=42)</td>
</tr>
<tr>
<td>Duration therapy, mo</td>
<td>15.2 ± 0.7</td>
<td>14.7 ± 0.9</td>
<td>17.1 ± 1.3</td>
<td>10.9 ± 1.2 a</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>74.0 ± 0.9</td>
<td>75.1 ± 1.2</td>
<td>73.0 ± 1.5</td>
<td>76.2 ± 1.6</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.9 ± 0.3</td>
<td>23.9 ± 0.3</td>
<td>24.1 ± 0.5</td>
<td>24.0 ± 0.5</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>62.6 ± 1.0</td>
<td>62.8 ± 1.4</td>
<td>62.2 ± 1.2</td>
<td>60.1 ± 2.0</td>
</tr>
<tr>
<td>Total fat, kg b</td>
<td>15.3 ± 0.6</td>
<td>16.5 ± 0.7</td>
<td>12.1 ± 0.9</td>
<td>24.1 ± 1.8 b</td>
</tr>
<tr>
<td>Total fat mass, kg b</td>
<td>10.9 ± 0.47</td>
<td>11.8 ± 0.52</td>
<td>8.4 ± 0.68</td>
<td>18.2 ± 1.8 b</td>
</tr>
<tr>
<td>Arm fat, kg b</td>
<td>1.24 ± 0.09</td>
<td>1.34 ± 0.11</td>
<td>0.83 ± 0.12</td>
<td>2.29 ± 0.28 d</td>
</tr>
<tr>
<td>Leg fat, kg b</td>
<td>2.28 ± 0.15</td>
<td>2.50 ± 0.17</td>
<td>1.75 ± 0.23</td>
<td>5.23 ± 0.60 d</td>
</tr>
<tr>
<td>Trunk fat, kg b</td>
<td>6.62 ± 0.24</td>
<td>7.08 ± 0.27</td>
<td>5.28 ± 0.32</td>
<td>9.62 ± 0.95 a</td>
</tr>
<tr>
<td>Central abdominal fat, kg b</td>
<td>1.42 ± 0.15</td>
<td>1.61 ± 0.21</td>
<td>0.99 ± 0.08</td>
<td>1.52 ± 0.16</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>4.1 ± 0.7</td>
<td>2.5 ± 0.3</td>
<td>5.3 ± 0.8 a</td>
<td>1.8 ± 0.2 a</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.1 ± 0.2</td>
<td>5.5 ± 0.2</td>
<td>7.1 ± 0.6</td>
<td>5.5 ± 0.2</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.0 ± 0.1</td>
<td>5.0 ± 0.1</td>
<td>4.9 ± 0.1</td>
<td>4.8 ± 0.1</td>
</tr>
<tr>
<td>Fructosamine, μmol/L</td>
<td>226 ± 3</td>
<td>227 ± 3</td>
<td>231 ± 5</td>
<td>226 ± 3</td>
</tr>
<tr>
<td>Insulin, mIU/L</td>
<td>10.07 ± 0.80</td>
<td>9.16 ± 0.85</td>
<td>11.5 ± 1.8</td>
<td>7.50 ± 0.83 f</td>
</tr>
<tr>
<td>Insulin resistance, mmol/L²</td>
<td>2.23 ± 0.20</td>
<td>2.07 ± 0.21</td>
<td>2.55 ± 0.45</td>
<td>1.58 ± 0.20 f</td>
</tr>
<tr>
<td>Leptin, ng/mL</td>
<td>2.48 ± 0.47</td>
<td>2.77 ± 0.47</td>
<td>2.28 ± 0.48</td>
<td>4.59 ± 1.9</td>
</tr>
<tr>
<td>C-peptide, mmol/L</td>
<td>2.87 ± 0.16</td>
<td>2.81 ± 0.21</td>
<td>3.01 ± 0.27</td>
<td>2.14 ± 0.16 a</td>
</tr>
<tr>
<td>Free fatty acids, μmol/L</td>
<td>589 ± 43</td>
<td>602 ± 65</td>
<td>612 ± 61</td>
<td>462 ± 52</td>
</tr>
</tbody>
</table>

*a HIV PI patients vs. HIV non-PI patients; P<0.01.
*b HIV PI patients vs. HIV non-PI patients; P<0.0001.
*c HIV PI patients vs. controls; P<0.0001.
*d HIV PI patients vs. controls; P<0.01.
*e HIV non-PI patients vs. controls; P<0.01.
*f HIV non-PI patients vs. controls; P<0.001.
}
Figure 4. Proposed mechanism of HIV protease inhibitor (PI)-induced peripheral lipodystrophy, hyperlipidemia, central obesity, breast hypertrophy, and insulin resistance. Solid bars, dashed arrows, and circled numerals, sites of PI action. The primary event is impaired generation of cis-9-retinoic acid (cis-9-RA) from retinoic acid (RA), either by direct binding to cytoplasmic retinoic acid binding protein type 1 (CRABP-1) (1) or by inhibiting cytochrome P450 3A isoforms that metabolize RA to cis-9-RA (2). This leads to reduced retinoid X receptor (RXR) stimulation and thus to apoptosis and impaired differentiation of peripheral adipocytes, with lipid release and/or reduced lipid storage. Inhibition of low density lipoprotein-receptor-related protein (LRP) would lead to reduced cleavage of fatty acids from circulating triglycerides by the LRP-lipoprotein lipase (LPL) complex on vascular endothelium (3) and reduced hepatic uptake of chylomicrons (4). The resulting hyperlipidemia would lead some fat to be redistributed to the abdomen (and, under the influence of estrogen, to the breasts), to insulin resistance, and to secondary type 2 diabetes mellitus in susceptible individuals. Inhibition of CRABP-2 would result in ectodermal dysplasia (ingrown toenails, dry lips and skin) (5). Inhibition of LRP would also block uptake of tissue plasminogen activator (tPA) and thus lead to increased bleeding in hemophiliacs (6). Modified from [18] by permission.

Future Research

A case definition for lipodystrophy syndrome is clearly required. Prospective studies will then be able to more accurately assess the syndrome’s incidence and severity and determine whether any clinical or biochemical parameter predicts the syndrome. Studies are required that examine lipodystrophy in women and children who are receiving PIs and that investigate whether lipodystrophy reverses on ceasing or switching antiretroviral regimens. Clearly, in vitro and in vivo studies are urgently required to explore the above hypothesis. A relevant animal model would be welcome.

Longer-term follow-up is required to assess whether vascular complications of insulin resistance and hyperlipidemia will develop and whether there is significant morbidity associated with long-term, severe fat depletion. Any role for dietary modification or lipid-lowering drugs for the treatment or prevention of lipodystrophy should be explored.

Newer HIV PIs are required that do not cause lipodystrophy,
hyperlipidemia, or insulin resistance. I would predict that PIs that bind neither CRABP-I nor LRP do not cause this syndrome. Of particular interest would be an assessment of the nonpeptidic PIs that are currently in early-phase development. Proteases from other pathogenic viruses, including hepatitis C and cytomegalovirus, have been proposed as targets for antiviral therapy. These proteins are serine proteases, which are more numerous than aspartyl proteases in humans.

Summary

Patients with advanced HIV disease clearly benefit from PI therapy, which slows the progression of disease, improves survival [2] and reverses some opportunistic infections [37]. Any survival advantage in early HIV disease, however, is unproven although biologically plausible and widely advocated [3, 4]. Alternative strategies for complete suppression of HIV replication, such as combining 2 nucleoside analogues with a nonnucleoside reverse transcriptase inhibitor [38], although perhaps less reliable, might be appropriate, particularly for those with low HIV viral loads. Cessation of PI therapy should be considered for patients for whom it has failed both virologically and clinically, if there is evidence of severe lipodystrophy or diabetes that requires therapy. Furthermore, patients with lipodystrophy have been mistakenly assumed to have HIV wasting syndrome, with all its psychological, social, and economic consequences.

Patients who are receiving HIV PIs frequently develop a syndrome of peripheral lipodystrophy, hyperlipidemia, and insulin resistance. This syndrome is common with prolonged therapy but overt diabetes mellitus seems to be relatively rare. The induction of hyperlipidemia and insulin resistance may lead to long-term cardiovascular disease. The manner in which this syndrome has been identified makes clear that as antiprotease agents are developed, we need more thorough interpretation of data gathered before drugs are licensed and more surveillance once drugs are marketed. Elucidation of the mechanisms underlying this syndrome should lead to new strategies to treat it and to the design of new PIs that do not cause it.

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