HIV protease inhibitors, the lipodystrophy syndrome and polycystic ovary syndrome—is there a link?

J D Wilson, R J C Dunham, A H Balen

A metabolic syndrome of insulin resistance, dyslipidaemia, central/visceral obesity, and peripheral lipodystrophy has been described with HIV protease inhibitors (PIs). A recent clinical presentation has led us to hypothesise that PIs can precipitate the metabolic changes associated with polycystic ovary syndrome (PCOS) by causing insulin resistance, and that people developing the metabolic/lipodystrophy syndrome may have genetic predisposition to PCOS.

In February 1997, a 37 year old woman presented with newly diagnosed HIV-1 infection, and a CD4 count of 80 cells ×10⁹/l. She began antiretroviral therapy with zidovudine, lamivudine, and saquinavir 600 mg thrice daily. She had a good response to treatment with a rise in CD4 count to 330 cells ×10⁹/l and a viral load <400 copies/ml, but found adherence to a three times daily regimen difficult. So in March 1998 her PI was changed to ritonavir 400 mg plus saquinavir 400 mg allowing twice daily dosing. In June 1998 she noticed dark hairs on her chin, upper lip, and cheeks, increasing abdominal girth, and a fat pad at the back of her neck. Her weight was stable at 57 kg. There were no recent changes in her menstrual cycle, which had a tendency to be erratic. She was nulliparous. Examination confirmed central obesity, a buffalo hump, and facial hirsutism. Her plasma follicle stimulating hormone (4.7 IU/l; normal range <8 IU/l) and luteinising hormone (22.3 IU/l; normal range <10 IU/l) were consistent with PCOS. Total serum testosterone level was normal (0.8 nmol/l; normal range 0.0–2.8 nmol/l), as were thyroid function tests, cortisol, and prolactin. Transvaginal pelvic ultrasound confirmed polycystic ovaries. Her fasting triglyceride (2.7 mmol/l) and cholesterol (7.4 mmol/l) levels were raised but blood glucose was normal. She chose electrolysis to control her hirsutism. So far she has decided to stay on the same antiretroviral treatment as she feels the side effects have not outweighed the clinical benefits.

The pathogenesis of PCOS is unknown but there is evidence of genetic susceptibility, possibly with autosomal dominant transmission with variable penetrance. Up to 20% of women may have the morphological appearance of polycystic ovaries on ultrasound. Women with PCOS are more likely to have hyperinsulinaemia and insulin resistance than weight matched controls, with decreased insulin sensitivity in peripheral tissues, particularly muscle and adipose tissue, but not in liver or ovary. The exact mechanism of insulin resistance is unclear but an intrinsic post-receptor defect has been identified. They are also more likely to have central/visceral obesity, with a significantly higher waist/hip ratio than age and weight matched controls. Obesity causes a more pronounced insulin resistance in women with PCOS than in controls. The hyperinsulinaemia stimulates production of ovarian androgens but inhibits synthesis of sex hormone binding globulin, resulting in increased free testosterone levels. It is the free testosterone that is biologically active. This may be elevated even when total testosterone is normal. A recent study has shown that PIs can precipitate the metabolic changes associated with polycystic ovary syndrome. Our patient would have been diagnosed as having lipodystrophy not PCOS had it not for the hirsutism. Male relatives of women with PCOS have been found to have insulin resistance, and a high frequency of non-insulin dependent diabetes and dyslipidaemia. Although the exact clinical,
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disorder (which has been reported in 11%12) suggest that development of the full metabolic syndrome, hyperlipidaemia, and diabetes mellitus with PIs.

Potential causes of the metabolic abnormalities and lipodystrophy with PIs have been suggested.10 11 Insulin resistance, hypertriglyceridaemia, and central obesity are interrelated so it is difficult to know which occurs first. Evidence is mounting that the initial factor is development of insulin resistance, which can lead to the other metabolic manifestations.11 This is probably the mechanism in those with mild lipodystrophy, which has been reported in up to 83% of people taking PIs.13 However, we suggest that development of the full metabolic disorder (which has been reported in 11%13) occurs in those with a genetic predisposition to insulin resistance (in the form of PCOS) when triggered by the additional insulin resistance caused by the PIs. Supporting this is the correlation of severity of lipodystrophy with insulin resistance,13 and the hyperandrogenaemia found in women with PI lipodystrophy.11 Women with hyperinsulinaemia but without PCOS do not get raised androgen levels.13 The improvement of the PI associated metabolic changes with metformin further supports insulin resistance as the primary problem.13 Similar responses to metformin have been described in women with PCOS, with reduction in insulin, lipoproteins, plasminogen activator inhibitor 1, central obesity, ovarian cytochrome P450c17α activity, and hence testosterone production.4 The reduction in testosterone following metformin for lipodystrophy again supports a linked abnormality of insulin action and androgen production in these individuals, as without this testosterone levels would not be expected to change.14 Lipodystrophy syndrome has been described in HIV disease without PIs. Our hypothesis supports this as any cause of increased insulin resistance—for example, other drugs, could precipitate the changes in the genetically susceptible. This genetic predisposition would explain why many people taking PIs have no metabolic disorder, and why there has been such a wide spectrum of clinical and metabolic manifestations described similar to the heterogeneity of PCOS.


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