New-onset diabetes mellitus associated with protease inhibitor therapy in an HIV-positive patient: case report and review

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A 56-year-old HIV-positive man presented to the hospital with a random blood glucose level of 27.4 mmol/L and a 3-week history of polyuria, polydipsia and polyphagia, accompanied by weight loss, fatigue, weakness and blurred vision. There were no symptoms of infection.

The patient had been diagnosed with HIV infection 7 years previously. His medical history included hypertension, diagnosed 20 years earlier, medication-induced painful peripheral neuropathy and chronic intermittent diarrhea. He had no history of opportunistic infection or endocrine disease. The patient's parents both had type 2 diabetes mellitus, and his father required insulin therapy.

Thirteen months before presentation the patient's CD4 count was 0.078×10^9/L and his viral load was 4.8 log HIV-1 RNA copies/mL (Chiron 2.0 assay; Chiron Corp., Emerville, Calif.). The protease inhibitor indinavir (800 mg every 8 hours) was initiated in combination with the reverse transcriptase inhibitors lamivudine (3TC, 300 mg twice daily) and zidovudine (AZT, 200 mg 3 times daily). Seven months later, after an initial response to the drug regimen, his viral load increased to baseline levels (5.4 log HIV-1 RNA copies/mL), and his drug therapy was changed to nelfinavir (750 mg 3 times daily), stavudine (d4T, 40 mg twice daily) and delavirdine, a non-nucleoside reverse transcriptase inhibitor (400 mg 3 times daily). Despite a partial response, with a CD4 count increase to 0.14×10^9/L and viral load decline to 4.62 log HIV-1 RNA copies/mL, antiretroviral therapy was discontinued 2 months later because of intolerable side effects, including diarrhea, rash and weight loss.

Two months before presentation the patient's CD4 count was 0.025×10^9/L and his viral load was 5.4 log HIV-1 RNA copies/mL. Antiretroviral therapy with lamivudine (150 mg twice daily), AZT (200 mg 3 times daily) and indinavir (800 mg every 8 hours) was started because he was intolerant to the other drug regimen and preferred a partially effective combination to no therapy. For prophylaxis of opportunistic infections, acyclovir (400 mg twice daily), fluconazole (100 mg twice daily) and trimethoprim–sulfamethoxazole (160/800 mg/d) were administered. The patient was also taking enalapril (10 mg orally twice daily) for his hypertension and testosterone intramuscularly for the previous 3 years to aid in weight gain.

Four years previously megestrol acetate (160 mg 3 times daily) had been initiated for weight loss, but it was taken for only 2 months. The megestrol was restarted 1 month before presentation because of a weight loss of 11.4 kg over the preceding 4 months, but it was discontinued after 1 week. Didanosine had also been taken 4 years previously but had been discontinued after 2 months because of an increase in the serum amylase level.

On presentation the patient's blood pressure was 145/100 mm Hg, his heart rate was 106 beats/min, and his respiration was normal. His body mass index was 21.9 (weight 71 kg, height 180 cm). There were no body habitus changes characteristic of lipodystrophy. There was evidence of volume contraction. He was alert and oriented, with no fever or signs of focal infection. Neurological examination revealed a mild tremor of the upper extremities; hyperesthesia and decreased pain, temperature and vibration sensation were noted in the lower extremities.

Laboratory results revealed the following levels: plasma glucose 27.4 mmol/L, sodium 128 mmol/L, chloride 93 mmol/L and amylase 68 U/L; the levels of creatinine, urea, potassium, carbon dioxide, alanine and aspartate aminotransferase and

alkaline phosphatase were normal. Results of blood and urine cultures were negative. The patient's CD4 count was 0.026×10^9/L and his viral load was 4.8 log HIV-1 RNA copies/mL. At 4 months before presentation the patient's random blood glucose level was 6.4 mmol/L, and at 1 month before it was 13.5 mmol/L. A chart review revealed normal levels over the previous 6 years.

On admission, the patient received 2 L of normal saline over the first 4 hours and normal saline supplemented with potassium chloride (40 mmol/L) at 250 mL/h for the next 5 hours. After overnight hydration, therapy with glyburide (2.5 mg orally) was initiated, and all antiretroviral drugs were discontinued. Glucose levels, monitored 4 times daily with a glucose meter, ranged from 13.9 to 17.6 mmol/L on day 1. By day 5 the dosage of glyburide was increased to 10 mg twice daily, and metformin (500 mg 3 times daily) was added; glucose levels ranged from 9.9 to 15.3 mmol/L.

On day 6 the oral hypoglycemic agents were discontinued, and premixed insulin 30/70 was initiated at a dose of 24 U before breakfast and 12 U before supper. The glucose levels on day 6 ranged from 6.1 to 7.9 mmol/L. On day 7 glyburide and metformin were restarted and insulin was discontinued because it was felt that the oral agents had not been given an adequate trial. Glucose levels on day 8 ranged from 6.9 to 9.9 mmol/L. The patient had a hypoglycemic episode (documented at 3.2 mmol/L) on day 9 because of a late lunch, and metformin was discontinued. At discharge on day 10, he was taking glyburide (10 mg twice daily) and had a blood glucose level of 6.3 mmol/L before breakfast and 7.6 mmol/L before lunch.

All oral hypoglycemic agents were gradually discontinued over the next 2 weeks. Results of a 75-g oral glucose tolerance test performed 1 month after discharge were negative by National Diabetes Data Group criteria;[1] the patient's fasting plasma glucose level was 5.4 mmol/L; his 2-hour plasma glucose level was 9.4 mmol/L, and the levels at 30, 60 and 90 minutes were less than 11.1 mmol/L. The patient's fasting (163 pmol/L) and post-glucose plasma insulin levels were higher than normal fasting levels.

Six weeks later the patient's CD4 count was 0.02×10^9/L and his viral load was 5.4 log HIV-1 RNA copies/mL. Antiretroviral therapy with saquinavir (400 mg twice daily), ritonavir (400 mg twice daily), AZT (300 mg twice daily), 3TC (150 mg twice daily) and ziagen (300 mg twice daily) was initiated. Within 3 weeks elevated blood glucose levels were detected by self-monitoring, and the patient was treated with glyburide (1.25 mg before breakfast and 2.5 mg before dinner). Although the glucose levels decreased, this was associated with fasting hyperinsulinemia (203 pmol/L), severe hyperlipidemia, a cholesterol level of 6.8 mmol/L, a triglyceride level of 10.8 mmol/L and a high-density lipoprotein level of 0.8 mmol/L (low-density lipoproteins were not measured because of the high triglyceride levels). Despite some improvement in his condition (CD4 count 0.03×10^9/L and viral load 4.8 log HIV-1 RNA copies/mL) the patient decided to discontinue all antiretroviral medications 3 months later because of diarrhea. Over the next month he was also able to taper and discontinue the glyburide.

Five months later the patient was still medication free, his fasting blood glucose was normal, the hemoglobin A_{1C} concentration was 5.9% (normally 4.1%–6.5%), the fasting insulin level 86 pmol/L, cholesterol 3.8 mmol/L, triglycerides 2.99 mmol/L, high-density lipoproteins 0.6 mmol/L and low-density lipoproteins 1.8 mmol/L. He had lost 2.5 kg, mainly from his abdominal region.

Comments

The unexpected onset of diabetes mellitus in a patient with HIV infection prompted a search for precipitating factors. A review of the patient's medication history revealed 2 drugs that could be implicated: megestrol acetate and indinavir. Megestrol acetate is a progestin and is commonly used as an appetite stimulant for the treatment of weight loss in patients with HIV infection and cancer.[2,3] There is in vivo[3] and in vitro[4] evidence to support a glucocorticoid mechanism of action for megestrol, and hyperglycemia, often reported within weeks of the initiation of megestrol therapy, is resolved in patients who discontinue treatment.[3] However, the role of megestrol in the onset of diabetes mellitus in this patient was probably limited, because the drug was only taken for 1 week in the month before his presentation, and hyperglycemia progressed after the drug was discontinued.

The other possible precipitating drug was indinavir. As of May 1997, 83 cases of diabetes or hyperglycemia in HIV-positive patients receiving protease inhibitor therapy were reported to the US Food and Drug Association.[5–9] A warning was therefore issued in June 1997 about the possible association between the 4 licensed protease inhibitors and hyperglycemia.[7] The Canadian experience has been similar. In July 1997 the Therapeutic Drugs Directorate at Health Canada reported that there were 8 cases of new-onset diabetes or a worsening of existing diabetes associated with protease inhibitor therapy.[10] However, because many of the patients had other medical conditions or were receiving other agents associated with the development of hyperglycemia, a causal relation between protease inhibitors and diabetes could not be established.[7,10] Of the 13 cases reported in various published letters,[6,8,9] the earliest onset of diabetes was 2 weeks after the initiation of protease inhibitor therapy and the latest onset was 12 months after, but most cases developed 1 to 6 months after the start of therapy. All of the patients were men, and approximately half had a family history of diabetes. None of the patients had ketoacidosis, although severe hyperglycemia with hyperosmolarity was observed. Diabetes resolved in the 2 patients who discontinued their protease inhibitor therapy;[6] the others were treated successfully with insulin, oral hypoglycemic agents or diet. Since glucose intolerance and new-onset diabetes have been associated with all protease inhibitors[5–10] it appears to be a drug-class effect.

Dever and associates[11] recently reviewed 105 cases of

protease inhibitor therapy in which the pretreatment blood glucose levels were available. Overt diabetes developed in 6 patients. In the remaining patients the mean blood glucose level was significantly higher than it had been before treatment, and in about 30% of patients it rose above 7.0 mmol/L. The data suggest that glucose homeostasis is adversely affected by protease inhibitors and that in some patients, possibly those predisposed to diabetes, symptomatic hyperglycemia develops.

The mechanism by which protease inhibitors may precipitate diabetes is unknown. Type 2 diabetes is associated with defects in insulin action and secretion.[12] There is evidence that insulin resistance occurs early in most patients and that the resistance is almost as severe in obese subjects with impaired glucose tolerance as it is in those with overt type 2 diabetes.[13,14] The conversion from impaired glucose tolerance to diabetes has been associated with an impairment in insulin secretion.[12,15] Thus, one might speculate that protease inhibitors act on pancreatic β cells to induce such a defect.

Insulin and other hormones must be cleaved by proteases from precursor polypeptides (e.g., proinsulin). Genetic defects in a serine endopeptidase catalyzing such activity have been associated with glucose intolerance.[16] However, the protease inhibitors used in HIV-positive patients block aspartate protease activity.[17] Although mammalian homologues have been identified,[18] these agents are very weak inhibitors of human aspartate proteases.[17] Furthermore, it is unknown whether these drugs inhibit any of the endogenous proteases that affect insulin processing or secretion.

Protease inhibitor therapy has also been associated with the development of hyperlipidemia, particularly elevated triglyceride levels, and changes in fat distribution, favouring the accumulation of visceral adipose tissue associated with lipodystrophy.[11,19–21] These lipid abnormalities in patients not infected with HIV are commonly associated with glucose intolerance and insulin resistance, even in the absence of overt diabetes.[14,22] In a recent report,[20] 65% of 116 HIV-positive patients were reported to have peripheral lipodystrophy with central adiposity after 10 months of protease inhibitor therapy. These patients had elevated triglyceride levels, increased insulin concentrations and insulin resistance. New-onset diabetes or a worsening of existing diabetes occurred in 2%. Carr and colleagues[21] postulated that protease inhibitors may interact with the low-density lipoprotein receptor-like protein (the scavenger receptor) because this receptor has a 70% homology with the catalytic site of the HIV protease that binds the inhibitors. Also, elevated triglyceride levels and lipodystrophy may be associated with elevated circulating levels of free fatty acids, which have been associated with insulin resistance[14,22] and impaired insulin secretion.[23]

In the case we have described, there was evidence of insulin resistance with elevated basal insulin concentrations, as well as hypertriglyceridemia and low high-density lipoprotein levels. These classic findings for patients with central obesity have been coined "syndrome X" or the metabolic syndrome[22] and are indicative of a predisposition for the development of type 2 diabetes. The oral glucose tolerance test performed 6 weeks after the indinavir therapy was stopped revealed a recovery from diabetes. Rechallenge with a combination of different protease inhibitors precipitated hyperglycemia, and discontinuation again resulted in remission.

These observations, combined with the data from the studies we reviewed, strongly support the notion that protease inhibitor therapy causes diabetes in some patients. An important aspect of prospective studies is the documentation of a change in fat distribution and of insulin resistance, because these are well established risk factors for diabetes. Since overt diabetes does not develop in all patients receiving protease inhibitor therapy, a genetic predisposition may play an important role in disease onset. However, it is unclear whether all patients with protease inhibitor-induced diabetes would eventually have hyperglycemia in the absence of this treatment. Our patient, like many others receiving treatment for HIV infection, was taking a variety of medications; we therefore cannot rule out a direct contribution of some other drug or an interaction between indinavir and another agent in the onset of diabetes in this patient. Other substances that have been reported to precipitate hyperglycemia are listed in Table 1 and have been reviewed elsewhere.[27]

In summary, protease inhibitor therapy may interfere with glucose homeostasis. Whether overt diabetes develops may depend on the predisposition of the individual and likely the ability of β cells to maintain adequate insulin secretion in the face of increasing insulin resistance. The

Table 1: Drugs implicated in hyperglycemia

Antihypertensives	**Hormones**
Furosemide	Corticosteroids
Beta-adrenergic blockers	Adrenocorticotropin
Calcium-channel blockers	Oral contraceptives
Diazoxide	Thyroid hormones
Minoxidil	Octreotide
Alpha-adrenergic blockers	Megestrol acetate
Acetazolamide	High-dose anabolic steroids
Lipid-lowering agents	**Psychotropic drugs**
Niacin	Phenothiazines
Bronchodilators	Levodopa/dopamine
Beta-2-adrenergic agonists	Chlordiazepoxide
Theophylline	Lithium
Immunosuppressive agents	Morphine
Cyclosporine	**Antibiotics/antimetabolites**
Tacrolimus[24]	Isoniazid
Antiretroviral therapy	Nalidixic acid
Pentamidine[25]	Rifampin
Protease inhibitors	Asparaginase
Didanosine[26]	**Toxins**
	Alcohol
	Vacor (rodenticide)
	Streptozocin
	Cyanide

mechanisms by which protease inhibitors act to produce this effect remains to be determined, but the condition appears to be reversible if protease inhibitor therapy is discontinued. Clinicians prescribing protease inhibitors may avoid hospital admission for patients with severe hyperglycemia by monitoring their blood glucose levels regularly and instituting early treatment when necessary.

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