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Effects of Recombinant Human Growth Hormone (r-hGH) and Protease Inhibitor Therapy on Glucose Metabolism in Patients with HIV and Associated Wasting.

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ABSTRACT

Objective: Hyperglycemia and glucose intolerance have been seen in patients (pts) prescribed protease inhibitors (PI)[1] , and mild transient elevations in serum glucose levels have been observed in patients taking recombinant human growth hormone (Serostim® [GH] for HIV-related wasting syndrome[2].

Methods: Reports on 6 HIV-infected caucasian men without prior histories of glucose intolerance who were treated with GH for HIV-related wasting and some of whom initiated highly active antiretroviral therapy that included a PI. An oral glucose tolerance test (OGTT) was given to all men with simultaneous determination of glucose and insulin levels. A follow-up (FU) OGTT was given to all pts between 7 and 12 months later. During this period all pts started GH to treat wasting, and 4/6 pts started Saquinavir therapy. At the FU OGTT 5/6 pts were still on GH, and one pt had interrupted GH therapy for one month.

Results: Mean age at baseline was 41.6yrs (range 33-49), mean HIV-RNA level was 13,966 copies/ml (range 245-456,699), and mean CD4 count 197 cells/mm^3 (range 0.0-998). The mean duration of GH and PI therapy at follow-up was 6.1 months (range 2.8-9.2), and 3.0 months (range 2.0 to 4.0) respectively. Results of the OGTT at baseline and FU were as follows;

	Baseline		Follow-up	
Time (hrs)	Glucose (mg/dL)	Insulin (mU/L)	Glucose (mg/dL)	Insulin (mU/L)
pre	106.7	9.0	95.8	13.0
0.5	145.5	82.3	142.2	102.4
1.0	142.7	91.3	137.0	117.2
2.0	104.3	41.0	107.5	82.0
3.0	70.8	11.5	75.2	17.3
4.0	79.0	6.1	79.2	11.1

Normal range: glucose: 70-105 mg/UL insulin: 10-26 mU/L

At FU the mean HIV RNA level was 3502 copies/ml, and mean CD4 count was 208 cells/mm^3.

Conclusion: The introduction of GH and PI therapy into the pts treatment regimens did not alter glucose tolerance, and glucose levels at baseline and FU were comparable to published values in healthy controls[4]. A slight increase in mean insulin levels was seen but this was due to one pt who exhibited hyperinsulemia at follow-up (glucose levels were comparable to baseline). The mean viral load was reduced at FU as would be expected with the use of PI therapy, however CD4 count was not greatly affected during this period. Further studies are needed to assess the frequency of hyperinsulinemia in patients on PI containing regimens, with and without GH therapy.

BACKGROUND

Alterations in glucose metabolism have been reported in HIV infected persons receiving Protease Inhibitors(PI). Hyperglycemia has been observed in HIV infected patients treated with all FDA approved PIs with incidences ranging from 10.7% with glucose level > 140mg/dl to 15.1% hyperglycemia >120mg/dL (Abstracts presented at 12th World AIDS Conference). Mild transient elevations in serum glucose levels have been observed in patients taking recombinant human growth hormone (r-hGH) for HIV related wasting syndrome (Daar, IDSA 1998). There is some concern that recombinant human growth hormone treatment in patients with HIV who were on concomitant PIs might precipitate diabetes mellitus.

Insulin/glucose ratio, which is predictive of induction of insulin resistance needs to be carefully monitored in all HIV patients, including those receiving PI and therapies such as growth hormone in HIV wasting. Monitoring is especially important in those patients with an underlying genetic predisposition to diabetes. Hyperglycemia is a prevalent side effect in some patients receiving PI and warrants routine monitoring of serum glucose. (Caldwell, Geneva 1998).

The use of r-hGH daily for 12 weeks does not result in clinically significant changes in glucose levels in patients with AIDS wasting on NRTIs. (Full prescribing Instructions/Package insert 10.2% Grade I-III). Short term treatment of patients with growth hormone did not significantly affect glucose tolerance, and results from long term studies have suggested that there is a successful adaptation of glucose and insulin levels to near baseline over time. (E. S. Daar, IDSA 1998).

OBJECTIVE

The objective of this retrospective analysis was to determine the effect on glucose metabolism in patients treated with growth hormone with the addition of a PI.

METHODS

Data was collected from patients in a private practice, assessing the therapeutic potential of human growth hormone in AIDS wasting between 1995 and 1997. All participants had a documented weight loss of at least 10% from their healthy weight.

A review was conducted of 10 HIV-infected Caucasian men without prior history of glucose intolerance being treated with Serostim for HIV-related wasting. Seven of the patients initiated PI therapy between May '95 and March '96. An oral glucose tolerance test (OGTT) was given to all men with simultaneous determination of glucose and insulin levels. A fasting blood sample was collected, after which a glucose solution (75 g) was drunk in a 5 minute period. Time zero was when the drink was consumed, and blood sampling was conducted at 30 minutes and then hourly intervals until 4 hours post OGTT. A follow-up (FU) OGTT was given to all patients between 8 and 12 months later. During this period all patients had initiated rhGH therapy to treat HIV-related wasting, and 7/10 patients had initiated Saquinavir therapy. At baseline all patients were on antiretroviral regimens (nucleoside reverse transcriptase inhibitors (NRTI)).

RESULTS

- Baseline ages ranged from 33 to 62 (mean 42.2 +/- 6.4) years
- Mean HIV-RNA was 144,288.5 (range 245-456,699)
- Mean CD4 count was 299.15 (range 0-998)

Baseline data are summarized in TABLE 1. All patients were receiving antiretroviral therapy throughout the study. The antiretroviral therapy administered at baseline are presented in Figure 1.

Table 1: Baseline: Age, HIV-RNA, CD4, and CD4%

Parameter	N	Mean	SD	Range
Age	10	42.2	+/- 6.4	(33, 62)
HIV-RNA	10	144,288.5	+/-188,818.3	(245 - 570,775)
CD4	10	299.15	+/- 276.11	(0.5, 998)
CD4%	10	16.3	+/- 11.86	(0.1 , 33.5)

Figure 1: Baseline: Antiretroviral Therapy

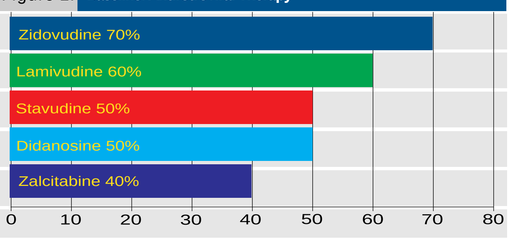

Table 2 Mean Glucose and Insulin Levels (n=10) Following OGTT Test

	Baseline (N=10)		Follow-up (N=10)	
	Glucose mg/dL	Insulin mU/L	Glucose mg/dL	Insulin mU/L
Baseline	98.9	8.43	96.8	14.05
1/2 Hour	150	73.28	151	88.34
1 Hour	136.1	73.05	140.6	104.82
2 Hour	104.4	37.77	114.3	71.13
3 Hour	75.6	14.39	77.5	14.31
4 Hour	76	5.71	83.7	10.2

- 7/10 patients were started on Saquinivar before the follow-up GTT. The glucose levels were comparable to baseline.
- One patient had hyperglycemia at baseline GTT, but at follow-up glucose returned to normal levels.
- 3/10 patients (without addition of a PI) at follow-up GTT. Only one of these patients had a baseline glucose of 131 at FU. He had been off of rhGH for 5 months. Subsequent random glucose monitoring showed no other incidence of elevated glucose (glucose>105 mg/dL).
- Hyperglycemia was reported in one patient on rhGH. This is consistent with the transient hyperglycemia (10.2%) reported in other studies of patients on GH (Daar, 1998).
- A slight increase in insulin levels were seen but this was predominantly due to one patient who exhibited hyperinsulemia at follow-up (glucose levels were comparable to baseline)

CONCLUSIONS

- The introduction of GH and Saquinavir into the patient's treatment regimens did not substantially alter glucose tolerance, and glucose levels at baseline and follow-up were comparable to published values in healthy controls.
- The concomitant treatment of rhGH (Serostim) in patients with AIDS-associated wasting and PIs has minimal affects on glucose metabolism.
- Glucose should be monitored carefully in setting of pre-existing hyperglycemia, especially with complex combinations of antiretroviral therapies that include protease inhibitors.

Figure 2: Individual GTT Result Summary (Patients 1-10)