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INCREASED tPA ANTIGEN LEVELS IN THE HIV LIPODYSTROPHY SYNDROME ARE REDUCED IN RESPONSE TO METFORMIN

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BACKGROUND: Cardiovascular disease (CVD) risk associated with the lipodystrophy syndrome remains unknown, but may be increased due to hyperlipidemia, hyperinsulinemia, increased visceral adiposity, and a prothrombotic state associated with these metabolic abnormalities.

OBJECTIVES: To characterize tissue-type plasminogen activator (tPA) antigen, a marker of impaired fibrinolysis and increased CVD risk, in lipodystrophic patients compared to controls. Furthermore, to examine the response of tPA antigen levels to treatment with metformin.

DESIGN: (i) Cross-sectional comparison: 86 patients (age=43.1±0.9 years, BMI=26.1±0.6 kg/m²) with the HIV lipodystrophy syndrome were compared to 258 age- and BMI-matched (age=43.7±0.5 years, BMI=26.2±0.3 kg/m²) subjects from the Framingham Offspring cohort. (ii) Treatment study: 25 HIV-infected patients with lipodystrophy and fasting insulin >15 µU/ml or impaired glucose tolerance, but without diabetes mellitus (age=44.8±1.4 years, BMI=27.3±0.8 kg/m², insulin=27.8±5.1 µU/ml) were enrolled in a placebo-controlled treatment study of metformin 500 mg orally, twice daily.

RESULTS: tPA antigen was significantly increased in patients with HIV lipodystrophy compared to Framingham control subjects (16.6±0.8 versus 8.0±0.03 ng/ml, $P=0.0001$). Among lipodystrophic patients, tPA antigen was highly correlated with fasting insulin ($R=0.30$, $P=0.004$) and the 120-min insulin to standard OGTT ($R=0.35$, $P=0.001$). In a

multivariate model, including age, sex, WHR, BMI and 120-min insulin, only gender and 120-min insulin were significant predictors of tPA antigen. In the treatment study, tPA antigen levels decreased 1.9 ± 1.4 ng/ml in the metformin-treated group and increased 1.4 ± 1.0 ng/ml in the placebo-treated group over 12 weeks ($P=0.02$ by ANOVA). Change in insulin AUC correlated significantly with change in tPA antigen ($R=0.43$, $P=0.03$).

CONCLUSIONS: tPA antigen, a marker of impaired fibrinolysis and increased CVD risk, is increased in association with hyperinsulinemia in the HIV lipodystrophy syndrome. Metformin reduces tPA antigen concentrations in the HIV lipodystrophy syndrome and could ultimately improve associated CVD risk.

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