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DISRUPTED EXPRESSION OF LIPID TRANSPORT GENES IN MONOCYTES OF INDIVIDUALS WITH HIV-ASSOCIATED LIPODYSTROPHY - AN ADDITIONAL RISK FOR CARDIOVASCULAR DISEASE?

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OBJECTIVES: Lipid accumulation within monocytes and macrophages, resulting in foam cell formation, is an important step in the development of atherosclerosis. Individuals exposed to antiretrovirals have abnormal expression of the transcription factors SREBP1 and PPAR γ in adipose tissue. ABCA1, a member of the ATP-binding cassette-transporter family, regulates efflux of cholesterol from monocytes, helping to prevent intracellular lipid accumulation and foam cell formation. Its expression is regulated by these transcription factors. We hypothesised that individuals with evidence of antiretroviral induced adipose abnormalities (lipoatrophy) would also have disruption of monocyte lipid regulation.

METHODS: CD14-positive magnetic beads were used to extract monocytes from whole blood of 20 HIV-infected individuals with lipoatrophy and 10 HIV-negative, healthy controls. RNA was extracted from the cells and semi-quantitative RT-PCR was performed on 20 ng samples of mRNA. The products were analysed on agarose gel and expression of SREBP1, PPAR γ , SCAP, ABCA1 and mitochondrial DNA was measured and compared to expression of a housekeeping gene (β -actin).

RESULTS: HIV-positive, lipoatrophic subjects had a significant decrease in the SREBP1 expression compared with controls, as measured by the SREBP1: β -actin ratio (0.41 versus 0.5, $P<0.01$). HIV-positive, lipoatrophic subjects with decreased SREBP1 expression also had significantly decreased ABCA1 expression ($r=0.65$, $P<0.01$). In multivariate analysis of treatment and disease related factors, decreased SREBP1

expression ($P=0.02$) and longer duration of exposure to lamivudine ($P=0.04$) correlated with decreased ABCA1 expression. There was no correlation between serum lipid subsets and expression of SREBP1, PPAR γ or ABCA1.

CONCLUSIONS: HIV-positive, lipotrophic subjects have decreased expression of SREBP1 and ABCA1 independent of serum lipids. This could affect lipid efflux from monocytes and lead to accumulation of intracellular lipid, foam cell formation and accelerated atherosclerosis in this group of patients.

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