Insulin resistance and adipose tissue

Korsheninnikova E/**, Nyman T**, Sutinen J***, Kannisto K*****, Silveira A*****, Gertow K*****, Fisher RM*****, Ehrenborg E*****, Eriksson P*****, Hamsten A*****, Funahashi T******, Matsuzawa Y******, Vidal H*******, Virkamäki A****, Yki-Järvinen H****

*Department of Molecular Cell Biology 2, LUMC, Leiden, **Minerva Research Institute, Helsinki, Finland, ***Divisions of Infectious Diseases and ****Diabetes, Department of Medicine, University of Helsinki, Helsinki, Finland, *****King Gustaf V Research Institute, Karolinska Institutet, Stockholm, Sweden, ******Department of Internal Medicine and Molecular Science, Osaka University, Osaka, Japan, *******Faculté de Medicine R Laennec, Lyon, France

Background: Abnormal lipid metabolism is a feature of the insulin resistance syndrome. Both subjects with excessive amounts of subcutaneous fat and patients with lipodystrophy, who lack subcutaneous fat, are at increased risk of developing insulin resistance, thus highlighting the importance of adipose tissue as regulator of insulin sensitivity.
Methods: Adipose tissue biopsies from HAART (highly active antiretroviral therapy)-treated patients with (n=30) or without lipodystrophy (n=13) were examined for mRNA expression of adipogenic transcription factors, fatty acid transport proteins, and adiponectin using real-time PCR. Liver fat content was measured by proton nuclear magnetic resonance spectroscopy.
Results: The expression of the adipogenic transcriptional regulators PPARγ, SREBP-1c and PGC-1 was reduced in lipodystrophic vs non-lipodystrophic patients (all $P < 0.05$). There were no differences in the expression of fatty acid transport proteins between the two groups. Adiponectin expression was also dramatically (~3-fold; $P < 0.001$) reduced in lipodystrophic subjects. Both serum adiponectin and mRNA levels correlated closely with features of insulin resistance, like liver fat content. Rosiglitazone treatment of lipodystrophic patients (24 wks; 8 mg/day) significantly increased the expression of PPARγ and PGC-1 (both $P < 0.05$), but did not affect SREBP-1c mRNA and expression of fatty acid transport proteins (FATP-1, FATP-4) compared to placebo. Rosiglitazone also significantly increased adiponectin mRNA and serum levels in lipodystrophic patients compared with placebo. The increase in adiponectin levels correlated with a reduction of hepatic fat content.
Conclusions: 1) Multiple alterations in gene expression in subcutaneous adipose tissue of HAART-lipodystrophic patients may contribute to development of lipodystrophy and insulin resistance in these patients. 2) Adiponectin deficiency may contribute to hepatic insulin resistance. 3) Rosiglitazone increased the expression of PPARγ, PGC-1 and adiponectin. 4) The increased expression of adiponectin might contribute to the amelioration of insulin resistance in lipodystrophic patients in response to rosiglitazone treatment.

Elena V. Korsheninnikova, Department of Molecular Cell Biology 2, Leiden University Medical Centre, Wassenaarseweg 72, 2333 AL Leiden, t 071 527 6856, e-mail elena@lumc.nl

Session 2