

Ineffective Suppression of Adipocyte Lipolysis in Metabolic Syndrome: An *in vivo* Test for Adipocyte Insulin Resistance

Jennifer Lynn Ford, The Pennsylvania State Univ, University Park, PA; **Raymond C Boston**, Univ of Pennsylvania Sch of Veterinary Med, New Bolton Center, PA; **Rachel E Walker**, **Gregory C Shearer**, The Pennsylvania State Univ, University Park, PA

Background: Insulin resistance is a major contributor to metabolic syndrome, disrupting both glucose and non-esterified fatty acid (NEFA) dynamics through ineffective glucose clearance and decreased suppression of lipid droplet lipolysis. The minimal model of glucose dynamics is used for glycemic insulin sensitivity however it does not measure adipocyte insulin sensitivity, the primary determinant of plasma NEFA. An in-vivo approach to measuring adipocyte insulin sensitivity using NEFA is employed, comparing healthy and metabolic syndrome subjects. Both the models are employed to estimate insulin sensitivity and validate the NEFA approach.

Objective: To test the use of NEFA kinetics to measure adipocyte insulin sensitivity compared to the glucose minimal model.

Approach and results: Metabolic syndrome (n=56) and optimally healthy (n=14) subjects underwent a frequently sampled intravenous glucose tolerance test, and plasma analyzed for insulin, glucose, and NEFA. Insulin sensitivity (S_I) and glucose effectiveness (S_G) were calculated from the glucose minimal model. S_I was $1.7 \text{ (mU/L)}^{-1} \text{ min}^{-1}$ and $0.40 \text{ (mU/L)}^{-1}/\text{min}^{-1}$ and S_G was 0.027 min^{-1} and 0.017 min^{-1} for the healthy and metabolic syndrome groups, respectively, indicating substantial glycemic insulin resistance in the latter. A model using glucose as the driver for NEFA kinetics was then applied. We found the initial rate of NEFA utilization by tissues (NU) was less, but the threshold glucose (tG) and glucose concentration required for a unit change in lipolysis inhibition (G_i) were greater in metabolic syndrome verses healthy (NU: $0.050[0.045, 0.057]$ vs. $0.068[0.054, 0.086]$ $p=0.03$; tG: $6.7[6.2, 7.2]$ vs. $5.0[4.3, 5.9]$ $p=0.001$; G_i : $0.30[0.25, 0.35]$ vs. $0.17[0.07, 0.27]$ $p=0.02$). No differences were found in initial rate of NEFA production or glucose utilization.

Conclusion: Our results indicate that suppression of lipid-droplet lipolysis requires greater stimulus in metabolic syndrome compared to insulin sensitive adipocytes. Further, the rate of NEFA removal is less in metabolic syndrome. These results reveal components of insulin sensitivity not demonstrated by the glucose model. The NEFA model provides a measurement of adipocyte insulin sensitivity not captured by glycemic indices.

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