Keynote Lecture 3

Chairperson

Moon-Kyu Lee
Eulji University, Korea

Speaker

Michael D. Jensen
Mayo College of Medicine, USA

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Education

Period	Affiliation	Position
– **1982-1985**	Mayo Graduate School of Medicine	Fellow
– **1980-1982**	Mayo Graduate School of Medicine	Resident
– **1980**	St. Luke's Hospital of Kansas City	Resident
– **1979**	U.M.K.C. School of Medicine	Medical Student

Affiliations / Experience

Period	Affiliation	Position
– **1985-Present**	Mayo Clinic	Consultant

Committee Memberships

- North American Association for the Study of Obesity/The Obesity Society
- American Society for Nutrition
- NIH Integrative Physiology of Obesity and Diabetes Study Section NIH Clinical and Integrative Diabetes and Obesity
- NHLBI Expert Panel to Update the Report on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults
- NIDDK DDK-E, beginning October

Publications

- Jensen MD, Haymond MW, Rizza RA, Cryer PE, Miles JM: Influence of body fat distribution on free fatty acid metabolism in obesity. *J. Clin. Invest. 83:1168-1173*
- Jensen MD: Gender differences in regional fatty acid metabolism before and after meal ingestion. *J. Clin. Invest. 96:2297-2303*
- Levine JA, Eberhardt NL, Jensen MD. Role of Non-exercise Activity Thermogenesis (NEAT) in Resistance to Fat Gain in Humans. *Science 283: 212-214*
- Nielsen S, Guo ZK, Johnson CM, Hensrud DD, Jensen MD. Splanchnic Lipolysis in Human Obesity. *J. Clin. Invest. 113: 1582 - 1588*
- Tchoukalova, Y, Votruba, SB, Tchkonia, T, Giorgadze, N, Kirkland, JL, Jensen, MD. Regional differences in cellular mechanisms of adipose tissue gain with overfeeding. *PNAS 107(42):18226-31*

Keynote Lecture 3

Human Adipose Tissue Metabolism: What Happens with Obesity

Michael D. Jensen (Mayo College of Medicine, USA)

Upper body/visceral obesity (UBO) is more strongly associated with metabolic abnormalities than is lower body obesity (LBO). The sine qua non of UBO is excess adipose tissue free fatty acid (FFA) release, especially under postprandial/hyperinsulinemic conditions, and these excess FFA undoubtedly contribute to the lipotoxicity of ectopic (liver, muscle, etc.) fat accumulation. In addition, UBO/T2DM is frequently accompanied by low grade adipose tissue inflammation and accumulation of senescent preadipocytes, but whether adipose inflammation related directly to the metabolic complications of UBO in humans by fueling adipose insulin resistance has not been examined in vivo. Because of the importance of FFA to whole body fuel metabolism, we have conducted studies that identified which adipose depot is primarily responsible for excess FFA in UBO. Although visceral fat is a predictor of excess FFA, it is not the source of excess FFA. Upper body subcutaneous fat accounts for ~75% of systemic FFA under basal and hyperinsulinemic conditions, with visceral and leg fat contributing lesser amounts. Excess FFA can cause insulin resistance by interfering with insulin signaling. It was unclear why upper body subcutaneous adipose fuel export is abnormal in UBO, but the preponderance of evidence from studies using rodent and cell culture models indicated that local inflammation was important. The data suggested that paracrine effects of cytokines, secreted by pro-inflammatory adipose tissue macrophages (ATM) interfere with adipocyte insulin signaling. If that is true in vivo, in humans, interventions to reduce inflammation would be a logical treatment strategy. We performed comprehensive measures of adipose inflammation and insulin regulation of lipolysis (the insulin concentration required to suppress lipolysis by 50% - IC50) in a large group of volunteers with a wide range of insulin resistance. We measured adipose insulin signaling at the level of Akt phosphorylation in relation to IC50 and studied the effects of lifestyle-mediated weight loss and 6 months of high dose omega-3 fatty acid supplements in a double-blind randomized trial.
From these studies we found that abdominal adipocyte size, but not total or pro-inflammatory macrophage burden, TNF, IL-6, IL-10 or IL-1β expression in abdominal fat is related to insulin resistance with regards to lipolysis (IC50). We found that the ability of insulin at postprandial concentrations to signal from the receptor through the Akt phosphorylation step is unrelated to IC50. We also reported that lifestyle-induced weight loss reduced (improved) IC50, but did not reduce adipose tissue macrophage content. In another study, we administered maximum dose omega-3 fatty acid supplements for six months, which reduced plasma triglyceride concentrations, but did not reduce adipose macrophage or senescent cell burden and did not improve IC50 . In summary, in humans with Class I-II obesity (BMI 30-39.9 kg/m2), adipose tissue inflammation and proximal insulin signaling are not linked to insulin resistant adipose lipolysis in UBO. We have ongoing studies designed to probe the causes of adipose insulin resistance in humans