SESSION 2
SELENIUM AND HUMAN HEALTH 1

EFFECT OF SELENIUM ON MARKERS OF RISK OF PRE-ECLAMPSIA IN UK PREGNANT WOMEN: A RANDOMISED, CONTROLLED PILOT TRIAL

M.P. Rayman [1], E. Searle [2], L. Kelly [3], S. Johnsen [1], S. Bath [1], J. Mao [1], C.W.G. Redman [2]

[1] University of Surrey, Guildford, United Kingdom
[2] University of Oxford, Oxford, United Kingdom
[3] University of Cork, Cork, Ireland

Background: Pre-eclampsia (PE) is a serious hypertensive condition of pregnancy associated with high maternal and fetal morbidity and mortality, characterized by oxidative stress, inflammation and endothelial activation leading to hypertension and proteinuria. Intake or status of selenium (Se) has been linked to its occurrence. We previously found that UK pregnant women in the bottom tertile of toenail Se were significantly more likely to have PE than the rest. Hence, we hypothesized that a small increase in the Se intake in pregnant women of inadequate Se status would protect against PE risk, as assessed by biomarkers.

Methods: In a pilot trial, we randomised 230 UK primiparous pregnant women of 12−14 weeks gestation to treatment with 60 mcg/d Se (as Se-yeast) or placebo. A blood sample was taken at trial entry and at 35 wks gestation and used to measure Se concentration; the remainder was separated into plasma/serum and used to measure selenoprotein P (SEPP1) and components related to PE risk. Our primary outcome measure was serum concentration of soluble vascular-endothelial-growth-factor-receptor-1 (sFlt-1), an anti-angiogenic factor that increases in PE.

Results: Whole-blood Se and plasma SEPP1 concentration were significantly higher at 35 weeks in the Se-group than in the placebo group. In line with our hypothesis, Se treatment of women in the lowest quartile of baseline Se status significantly lowered sFlt-1 (P=0.039). When the outcomes of pre-eclampsia and the related pregnancy-induced hypertension (PIH) were combined, Se treatment significantly reduced the odds of having PE/PIH in all participants (OR 0.350; 95% CI 0.126, 0.974; P=0.044).

Conclusion: Pregnancy appears to be putting pressure on the Se stores of UK women who have marginal Se status. Though our pilot trial was limited by power, Se supplementation did reduce sFlt-1, a marker of PE risk, in women of low Se status. The suggestive effect on risk of PE/PIH needs to be explored in a larger trial.

THE DEBATE ON SELENIUM AND TYPE 2 DIABETES MELLITUS

H. Steinbrenner

Heinrich-Heine-University Duesseldorf, Institute for Biochemstry and Molecular Biology I, Duesseldorf, Germany

Recent data from epidemiological and animal studies have suggested potential pro-diabetic effects of supranutritional Se intake. However, several randomized controlled studies yielded inconsistent results and longitudinal studies did not support a causal role of Se for development of type 2 diabetes mellitus in humans. Se concentrations in the habitual diet and in dietary supplements are probably not sufficient to induce overt diabetes in healthy individuals. On the other hand, high plasma Se and selenoprotein P (Sepp1) levels have been found to be associated with biomarkers of an impaired carbohydrate and lipid homeostasis in diabetes patients. As hepatic biosynthesis of Sepp1 is suppressed by insulin and stimulated under hyperglycemic conditions, these cross-sectional associations might derive from a side-effect of the dys-regulated carbohydrate metabolism in diabetes. Conversely, dietary Se oversupply may result in hyperinsulinemia and decreased insulin sensitivity. The Se transport and supply protein Sepp1 and the hydrogen peroxide-reducing selenoenzyme glutathione peroxidase 1 (GPx1) are capable of interfering with insulin-controlled metabolic pathways. A probable rationale derives from the positive and negative regulation of both glucose-induced insulin secretion and insulin-induced signaling by hydrogen peroxide. Se status and GPx1 expression have been reported to affect insulin-antagonistic phosphatases that are regulated by hydrogen peroxide-mediated reversible oxidation of catalytic cysteine residues. GPx1 and Sepp1 may impair the activity of key mediators in energy metabolism such as protein kinase B (Akt) and AMP-activated protein kinase (AMPK) in liver and skeletal muscle.

Conclusion: Overabundant expression of antioxidant selenoproteins such as GPx1 and Sepp1 may affect the insulin-regulated energy metabolism. Therefore, individuals with high Se status or (pre)diabetes should not consume Se-containing dietary supplements.

ENHANCED ADIPOSE TISSUE MASS AND FUNCTION IN HUMAN SELENOPROTEIN DEFICIENCY DUE TO ROS-MEDIATED PPARg ACTIVATION

E. Schoenmakers [1], C. Moran [1], N. Schoenmakers [1], M. Agostini [1], C. Mitchell [1], O. Rajanayagam [1], M. Dattani [2], F. Karpe [3], L. Hodson [3], K. Chatterjee [1]

[1] University of Cambridge, Institute of Metabolic Science, Cambridge, United Kingdom
[2] Great Ormond Street Children's Hospital, London, United Kingdom
[3] Oxford Centre for Diabetes, Endocrinology & Metabolism, Oxford, United Kingdom

We have previously described two unrelated male subjects (P1,42yrs; P2,8yrs) with defects in *SECISBP2*, resulting in generalized selenoprotein deficiency. The associated multisystem phenotype includes reduced T4 to T3 conversion, myopathy and increased cellular reactive oxygen species (ROS) with oxidative damage; P1 exhibits azoospermia, impaired T-cell proliferation and photosensitivity.

Patients have a distinct metabolic phenotype, with increased total body and subcutaneous fat mass but normal visceral adipose tissue, favourable fasting insulin and lipid profiles, low intrahepatic lipid content (P1), and high adiponectin levels. In vivo metabolic studies (P1) demonstrate low fasting plasma triglyceride levels, with little excursion postprandially but exceptionally high postprandial total and dietary triglyceride uptake by subcutaneous adipose tissue. Fasting free fatty acid levels were initially very high but suppressed quickly following meals. These findings are consistent with rapid, efficient highly insulin sensitive fatty acid esterification in his adipose tissue.

Murine Secisbp2-deficient preadipocytes exhibit increased ROS and enhanced adipose differentiation, reversed by antioxidants. Early adipogenic markers are unchanged, but PPARγ target genes mediating adipogenesis and lipogenesis are upregulated, suggesting enhanced PPARγ activation. Similar enhanced adipogenesis and PPARg target gene expression was seen in primary pre-adipocytes from our *SECISBP2* patients. Conditioned medium from murine Secisbp2-deficient adipocytes mediates enhanced PPARg activation in a heterologous cellular reporter system, linking raised ROS with generation of PPARg ligands, as has been suggested previously.

Overall, we suggest that increased subcutaneous adipose mass and function in the SECISBP2-deficient patients is a cell autonomous phenotype dependent on increased ROS levels, resulting in enhanced PPARγ activation driving adipogenesis, lipogenesis and insulin sensitisation.

SELENOCYSTEINE LYASE IN METABOLIC SYNDROME

L.A. Seale, A.C. Hashimoto, S. Kurokawa, C.L. Gilman, A. Seyedali, F.P. Bellinger, A.V. Raman, M.J. Berry

University of Hawaii at Manoa, Cell and Molecular Biology, Honolulu, United States

The impact of selenium (Se) on energy metabolism and its relationship with metabolic disorders remains a controversial topic, with evidence pointing to either a protective or causal effect, depending on the methodology used. Several selenoproteins and selenoprotein synthesis factors have been implicated in regulation of energy metabolism in rodents and humans. Selenoprotein translation requires *de novo* synthesis of the unique aminoacid selenocysteine (Sec). This process is enabled by selenoprotein degradation followed by breakdown of the Se to reenter its biosynthesis cycle. The enzyme Sec lyase (Scly) catalyzes the Se recycling reaction by breaking down Sec, and is found mostly in the liver of mammals. We previously demonstrated that the Scly knockout (KO) mouse model develops metabolic syndrome when fed a low Se diet (0.08 ppm).

This is accompanied by alterations in hepatic levels of insulin signaling regulator PTP1B and lipogenesis coordinator acetyl-CoA carboxylase 1 (ACC1) phosphorylation. We recently fed Scly KO mice a high-fat diet (45% kcal lipid) with adequate levels of Se (0.25 ppm) for at least 10 weeks. This diet increased the body weight of Scly KO mice more rapidly, and led to more accumulation of fat in their inguinal depots and in the interescapular brown fat than their wild-type counterparts on the same diet. Scly KO mice also worsened their metabolic phenotype, with severe glucose intolerance, hyperinsulinemia, hypercholesterolemia, increased lipid peroxidation, higher levels of circulating selenoprotein P, and worsened non-alcoholic fatty liver disease when compared to their wild-type counterparts. Levels of ACC1 were also increased in these mice, indicating a potential stimulation of the lipogenic pathway in this organ. Our results highlight the importance of Se recycling pathways in fat metabolism and homeostasis in rodents, and will be discussed in light of the role of Se metabolism in aggravation of obesity.