SESSION 15
SELENIUM IN THE CLINICS

SELENIUM AND CANCER PREVENTION: WHO MAY BENEFIT FROM INCREASED SELENIUM INTAKES?

G.F. Combs, Jr.

USDA, Grand Forks Human Nutrition Research Center, Grand Forks, United States

Virtually all animal and cell model studies have shown Se to reduce cancer risk in non-deficient subjects. However, the largest trial, SELECT, found no protection against prostate cancer in subjects of relatively high Se status (plasma Se 136 ng/mL). Those results are *not inconsistent* with the NPC trial, which found supplemental Se to have *no* benefits for subjects with plasma Se levels >120 ng/mL, reducing cancer risk only for those in the lowest tertile (< 106 ng/mL). This suggests that supplemental Se can reduce cancer risk for individuals of low-to-adequate Se status, plasma Se 70-106 ng/mL - a range that includes a fifth of Americans, most Europeans and many others. Other factors may also be important determinants of the antitumorigenic efficacy of Se. Utilization of SeMet differs between men and women and by GPX1 genotype, and genetic variants of GPX4 and SeP have been linked to colorectal cancer risk. Obesity can promote cell proliferation, survival and cancer progression pathways that are inhibited by Se; it is also likely to reduce synthesis of the putative active metabolite CH_3SeH. We have found obesity to reduce the antitumorigenic efficacy of Se in our animal model of 2^o carceningenesis. Se may also affect the metabolic output of the gut microbiota, as it is required by several methanogenic *Archaea* and gram+ bacteria that have selenoenzymes and are growth-limited by Se supply. We found Se to promote hindgut fermentation, increasing output butyrate, thought to protect against colonic tumorigenesis. Research addressing roles of these and, perhaps, other factors in affecting the antitumorigenic potential of Se changes the question that for years has driven this field, i.e., 'does Se prevent cancer?' to a more salient and useful one: 'Who can benefit from increased Se intake?'

SELENIUM METABOLISM IN AUTOIMMUNE DISEASES

L. Schomburg

Charité - Universitätsmedizin Berlin/Institut für Experimentelle Endokrinologie, Berlin, Germany

The personal selenium (Se) status and several selenoproteins affect inflammation and immune responses. Low Se concentrations have been described in patients with autoimmune diseases (AID), e.g. rheumatoid arthritis or autoimmune thyroiditis. The underlying mechanisms remain enigmatic. An adjuvant supplementation with Se has proven beneficial in some but not all respective clinical trials. We have shown that the down regulation of central factors of the selenoprotein biosynthesis machinery may contribute to a declining Se status under inflammatory conditions. Here, we hypothesize that autoimmunity against such limiting factors may compromise the regular Se status in AID.This notion is supported by several studies from diverse clinical research areas. SEPSECS was initially identified as the soluble liver antigen/liver pancreas antigen (SLA/LP) in autoimmune hepatitis. The autoantibody (aAB)-mediated inhibition of SEPSECS activity may explain serum Se deficiency in this disease. SePP transports Se to target tissues where it is taken up in a receptor-mediated process involving LRP2 or LRP8. Accordingly, specific aAB against LRP2 have been described in nephrotic syndrome and some systemic AID. Intracellular metabolism of Se may involve two Se-binding proteins (SeBP), the 56 kDa SeBP1 and 14 kDa FABP1. In fact, aAB against SeBP1 are widespread in AID and of specific diagnostic value in Behcet's disease. We have developed novel aAB assays for FABP1, SeBP1 and SePP, and will report on the relative prevalence of such aAB in human sera, their activities and potential pathological relevance. Further studies with samples from patients suffering from different AID will be conducted in order to test whether these aAB correlate to the patients' Se deficit, and to discuss whether a personalized monitoring and adjuvant Se supplementation should be considered in order to avoid a disease-aggravating Se deficit in patients with AID.Supported by the BMWi, DFG and Deutsche Krebshilfe.

RANDOMISED, CONTROLLED PILOT TRIAL OF SELENIUM SUPPLEMENTATION ON THYROID FUNCTION IN UK PREGNANT WOMEN

J. Mao [1,2], S.C. Bath [1], V.J. Pop [3], H.L. Vader [4], C.W. G. Redman [5], M.P. Rayman [1]

[1] University of Surrey, Faculty of Health and Medical Sciences, Guildford, United Kingdom
[2] The First Hospital of China Medical University, Institute of Endocrinology and Department of Endocrinology and Metabolism, Shenyang, China
[3] Tilburg University, Tilburg, Netherlands
[4] University of Technology, Eindhoven, Netherlands
[5] John Radcliffe Hospital, University of Oxford, Oxford, United Kingdom

Selenium (Se) is important for human health and has a particular role in immune and thyroid function. Maternal thyroid function directly influences fetal development. We explored the effect of Se supplementation on thyroid function in UK pregnant women. At 12 wks' gestation, 230 pregnant women were randomized to 60 µg/day Se (as Se-yeast) or placebo-yeast in the SPRINT trial, and remained on treatment until the end of pregnancy. We measured whole-blood Se at 12 and 35 wks, plasma selenoprotein P (SEPP1) at 35 wks, serum thyroid-stimulating hormone (TSH), free thyroxine (FT4) and antithyroid peroxidise antibodies (TPOAb) at 12, 20 and 35 wks. Whole-blood Se levels did not differ between the Se and placebo groups at baseline. At 35 wks, both whole-blood Se and plasma SEPP1 levels were significantly higher in the Se group than in the placebo group (both, $P< 0.001$). Plasma SEPP1 level at 35 wks was positively correlated with whole-blood Se (Spearman's r=0.776, $P< 0.001$) in the whole population reflecting the fact that even in many of the women allocated to Se treatment, SEPP1 did not reach a plateau.

We explored the effect of Se supplementation on TPOAb titre on which Se has been shown to have a beneficial effect. In TPOAb+ women: (i) the titre significantly decreased in both treatment groups with no difference between groups; (ii) TSH significantly decreased in both treatment groups but the pattern of change was different; (iii) FT4 also decreased, but to a greater extent in the Se group than the placebo group ($P< 0.01$), suggesting that Se supplementation might increase T4 to T3 conversion.Although TSH increased and FT4 decreased in both Se and placebo groups ($P< 0.001$), there was no difference between groups. In the placebo group, the change in FT4 was positively correlated with the change in whole-blood Se (Spearman's r=0.233, p=0.015), suggesting a possible connection between Se and thyroid hormone metabolism in pregnancy, as in critical illness.

SELENIUM STATUS PARAMETERS IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME

P. Zagrodzki [1], M. Krzyczkowska-Sendrakowska [2], F. Nicol [3], R. Wietecha-Posluszny [4], T. Milewicz [2], J. Kryczyk [5], J. Krzysiek [2]

[1] Jagiellonian University Medical College, Dept. of Food Chemistry and Nutrition / H. Niewodniczanski Institute of Nuclear Physics, Krakow, Poland
[2] Jagiellonian University Medical College, Dept. of Gynecological Endocrinology, Krakow, Poland
[3] The University of Aberdeen, Rowett Institute of Nutrition and Health, Vascular Health Division, Aberdeen, United Kingdom
[4] Jagiellonian University Faculty of Chemistry, Dept. of Analytical Chemistry, Krakow, Poland
[5] Jagiellonian University Medical College, Dept. of Food Chemistry and Nutrition, Krakow, Poland

Polycystic ovary syndrome (PCOS) is considered to be the most common endocrine disorder in women of reproductive age. To date, no systematic study of interactions between selenium status parameters, thyroid function parameters, sex hormones and other relevant laboratory parameters in patients with PCOS has been undertaken.

Aim of the study: To compare selenium status parameters levels in women with PCOS and in the control group, and to investigate the multidimensional interactions between the mentioned groups of parameters.The subjects (n=28, 25.4 y) were diagnosed with PCOS according to the AES criteria. Female patients visiting Dept. of Gynecological Endocrinology due to PCOS unrelated problems and having normal menses were recruited into the control group (n=70, 26.8 y). Two other groups involved PCOS and Hashimoto disease (HD) patients (n=13, 27.3 y) and the controls with HD (n=10, 26.2 y) displaying no other concomitant diseases. The following parameters were investigated: (1) plasma Se, GPX3 and SelP; (2) TSH, fT3, fT4; (3) TT, E2, DHEAS, SHBG, LH, FSH, PRL), (4) OGTT with insulinemia, vit. D3, serum Ca. The indexes: FAI, HOMA-IR, and LH/FSH were calculated. The interactions between parameters were investigated by means of PLS method. None statistically significant differences with respect to Sel P or GPX3 between the 4 studied groups were found, though such differences were noticeable for TT, SHBG, FAI, insulin profiles at 0 and 60 min., and DHEAS. The correlation between TT and DHEAS was found the strongest. The other group of mutually highly and positively correlated parameters consisted of GPX3, FSH, fT3, fT4. All the latter parameters correlated negatively with vit. D3. No apparent differences in selenium status between healthy subjects and patients with PCOS, also compli-

cated with HD, were identified. GPX3 took part in interactions with fT3, fT4, vit. D3 and FSH. The PLS model still remains open for further investigation in patients with PCOS and/or HD.

FUNCTIONAL AND REGULATORY ADAPTATIONS TO LEVELS OF DIETARY SELENIUM IN RECENT HUMAN HISTORY

L. White, F. Romagné, A. Weihmann, A. Andrés, S. Castellano

Max Planck Institute for Evolutionary Anthropology, Department of Evolutionary Genetics, Leipzig, Germany

As humans spread out of Africa about 60,000 years ago and migrated around the world, they came to inhabit a vast range of environments. These environments differ widely in their selenium levels in the soil and this, coupled with cultural variation in dietary practices, has led to a wide range of selenium intake levels in populations around the world. Both excess and deficiency of dietary selenium can have adverse health consequences in humans. Indeed, the prevalence of selenium-related diseases (Keshan disease, Kashinbeck disease, thyroid imbalance, increased susceptibility to infections, decreased fertility and others) often reflects the geographic distribution of this trace element in human nutrition. Thus, shifts in dietary selenium intake sustained over many generations are a likely selective pressure in humans. To explore this possibility we have conducted a survey of worldwide variation in human selenium related genes. We have captured and re-sequenced 52 genes, that either incorporate selenium or are involved in its metabolism, in 928 individuals from 52 populations from Africa, Middle East, Europe, Asia, Oceania and America. We have identified signals of genetic adaptation in both selenoprotein genes and genes involved in selenium homeostasis or selenocysteine insertion into proteins. Thus, both the function and regulation of selenium and selenoproteins may have adapted to changes in selenium status in humans. In addition, signatures of adaptations are particularly strong at genes in populations from regions of the world with extreme levels of selenium in the soil or diet. This suggests that migration into environments with excess or deficiency of selenium has shaped recent human evolution, and that functional and regulatory adaptations may have moderated the health effects of impaired selenium status in humans. Further, it is possible that such adaptations resulted in human populations today having different risks of selenium-related diseases.

mRNA EXPRESSION OF SELENOPROTEINS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

J. Molnár [1], O. Galamb [2], F. Sipos [2], K. Tóth [2], K. Leiszter [2], B. Wichmann [2], Z. Tulassay [2,3], B. Molnár [2,3]

[1] Molzsa Medical Kft., Budapest, Hungary
[2] Semmelweis University, 2nd Department of Medicine, Budapest, Hungary
[3] Hungarian Academy of Sciences, Molecular Medicine Research Group, Budapest, Hungary

Introduction: Serum selenoprotein P levels have been reported to be decreased in patients with Crohn's disease. However, there are few data regarding mRNA expression of selenoproteins in patients with inflammatory bowel disease (IBD). Therefore, the aim of our study was to assess and compare mRNA expression of selenoproteins in both colonic biopsy and blood samples of IBD patients and healthy controls.

Materials and methods: mRNA expression of selenoproteins of colonic biopsies (n=24) and blood samples (n=5) of patients with Crohn´s disease and patients with ulcerative colitis (n=25 and 6, respectively) were determined using Affymetrix HGU133 plus 2.0 microarrays and compared with results of healthy controls (n=49 and 16, respectively). Statistical analysis was performed using the Tukey HSD test.

Results: In biopsy samples, mRNA expression of three selenoproteins was lower in both Crohn´s disease and ulcerative colitis compared to healthy samples: glutathione peroxidase (GPx) 3, selenoprotein W, selenophosphate synthetase 2 (all $p< 0.01$). In contrast, mRNA expression of five selenoproteins was higher in IBD compared to healthy samples: GPx 1, 15 kDa selenoprotein, selenoprotein M, selenoprotein N, selenoprotein X (all $p< 0.05$). mRNA expression of GPx 2 was higher in biopsy samples from patients with ulcerative colitis compared to healthy subjects ($p=0.005$) but not in Crohn´s disease. In blood samples, mRNA expression of selenophosphate synthetase 2 was higher, while mRNA expression of selenoprotein T was lower in healthy subjects compared to IBD patients.

Conclusions: Although mRNA expression of the majority of selenoproteins was similar in IBD patients and healthy subjects, some selenoproteins are downregulated while certain selenoproteins are upregulated possibly indicating a specific role. Our results still need to be verified by RT-PCR and immunohistochemistry.