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High selenium intake is associated with endothelial dysfunction: critical role for endoplasmic reticulum stress

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Background: Selenium is an essential trace element important to human health. Nonetheless, supra-nutritional selenium intake is reported to be associated with insulin resistance[1] and may therefore increase the risk of diabetes and disrupt endothelial function (ED), the initial step in atherosclerosis development. However, the underpinning molecular mechanisms are not clear. High selenium concentrations cause apoptosis in cancer cells through the induction of endoplasmic reticulum (ER) stress[2], a mechanism also involved in the pathogenesis of ED[3]. Therefore, we hypothesised here that high selenium intake could cause ED through the activation of ER stress response.

Method: Human Umbilical Vein Endothelial Cells (HUVECs) were cultured with selenite at either physiological (0.5µM) or supra-nutritional concentrations (5-20µM) for 8 to 24 hours in the presence or absence of a chemical chaperone, 4-phenylbutryic acid (PBA). Then, mRNA expression of key ER stress response markers was analysed by qPCR. To assess endothelial function, we evaluated NO (Griess assay) release and Reactive Oxygen Species (ROS, flow cytometry) production. Finally, apoptosis (flow cytometry) and caspases 3/7 activity were measured.

Results: High selenium concentrations (5-20µM of selenite) compared to physiological concentration (0.5µM) or control enhanced mRNA expression of several ER stress markers such as CAAA/enhanced-binding homologous protein (CHOP) [control (2.25±0.88), 0.5 µM (3.9±0.85), 10µM (36.2±6); n=5]. The pre-incubation of cells with PBA completely reversed high selenium-mediated ER stress. High selenite (5-20µM) also reduced NO production [control (2.27±0.07), 0.5µM (2.4±0.04), 10µM (1.8±0.05); n=5] and enhanced ROS production [control (18.9±1.93), 0.5µM (21.7±2.14), 10µM (68±0.65); n=5] compared to physiological concentration of selenite while cells pre-treated with PBA were fully protected. Finally, supra-nutritional concentrations of selenite increased the percentage of apoptotic HUVECs [control (2.96%±0.94), 0.5µM (3.92%±0.85), 10µM (43.7%±5.1); n=7] and augmented caspases 3/7 activity [0.5µM (0.45±0.08), 5µM (1.92±0.3) fold of control; n=5] compared to physiological concentration. Importantly, pre-treatment of cells with PBA completely reversed high selenium-mediated cell death.

Conclusions: We show here that high selenium treatment causes ED and cell death through the activation of ER stress. These results highlight the importance of a balanced selenium intake in order to achieve maximal health benefits. These findings underscore the importance to monitor cardiovascular risk development in cancer patients supplemented with high amounts of selenium as part of their chemotherapeutic intervention.

References: 1. Bleys J et al. (2007) *Diabetes Care* **30**:829-834. 2. Wallenberg M et al. (2014) *J Cell Mol Med* **18**:671-684. 3. Kassan M et al. (2012) *Arterioscler Thromb Vasc Biol* **32**:1652-1661.