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## Health and Biomedical Pillar

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### High Selenium Intake is Associated with Endothelial Dysfunction: Critical Role for Endoplasmic Reticulum Stress

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Selenium is associated with insulin resistance and may therefore affect endothelial function, increasing type II diabetes risk and associated cardiovascular-disease risk. However the underpinning molecular mechanisms involved are not clear. High selenium doses cause apoptosis in some cancer cells through the induction of endoplasmic reticulum (ER) stress response, a mechanism also involved in the pathogenesis of insulin resistance and endothelial dysfunction (ED). Thus we hypothesised that high selenium intake could cause ED through ER stress.

Endothelial cells were treated with selenite (0.5–20  $\mu$ M) in the presence or absence of the ER chemical chaperone, 4-phenylbutyric acid (PBA). High selenium concentrations (5–10  $\mu$ M of selenite) compared to physiological concentration (0.5  $\mu$ M) enhanced mRNA expression of several pro-apoptotic ER stress markers; such as activating transcription factor-4 (ATF4) and CAAA/enhanced-binding homologous protein (CHOP). In addition, Griess assay showed that high selenite treatment (5–20  $\mu$ M) reduced NO production. Moreover, flow cytometry assays showed that high selenium enhanced ROS production and apoptosis in cells. Finally, supra-nutritional concentrations of selenite increased caspases 3/7 activity in endothelial cells compared to the physiological concentration. Interestingly, the pre-incubation of cells with PBA completely reversed all the effects of high selenium indicating the involvement of ER stress response.

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

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