EDITORIAL

Might Oral Zinc Protect Pancreatic B-Cells Against Oxidative Insults?

Mark L. Failla, PhD

Department of Nutritional Sciences, The Ohio State University, 1787 Campbell Hall, Columbus, OH 43210-1295

Type 1diabetes is an acute onset autoimmune disease caused by the destruction of the insulin-producing pancreatic β-cells. Autoimmune, viral, environmental and dietary factors can trigger the pathogenic process, although mechanisms leading to the selective destruction of the β-cells remain largely unclear. Elucidation of the pathways leading to the injury and death of β-cells are needed to develop protective and therapeutic strategies for the prevention or attenuation of damage induced by diabetogenic agents. The possibility that the low level of expression of antioxidant enzymes in β-pancreatic cells increases their sensitivity to oxidative insults has provided the impetus for a series of recent studies addressing the impact of antioxidant supplementation on pancreatic health.

The essential trace metal zinc represents a dietary "antioxidant" that was recently shown to delay the onset of spontaneous diabetes in the BB Wistar rat (1). Bray and associates (2) have extended this line of inquiry to determine if dietary zinc supplementation would similarly protect mice against chemically induced diabetes. Mice were fed the standard AIN93G rodent diet containing either control (50 ppm) or high (500 or 1000 ppm) zinc for two weeks before injection of one of two standard diabetogenic compounds. The administration of multiple low doses of streptozotocin induces infiltration of lymphocytes and macrophages that secrete cytokines and reactive oxygen species that damage and kill β cells. In contrast, alloxan appears to induce the necrotic demise of β cells by the generation of reactive oxygen species during its metabolism. Dietary zinc supplementation markedly limited the extent of chemically induced islet cell death and infiltration of immune cells, and attenuated changes in blood glucose and insulin of test mice. This protection was associated with several fold increases in the concentration of zinc in plasma and pancreas, without any affects of high zinc on food intake, body weight gain or tissue copper content. The possibility that zinc mediates its protective effect by blocking a central oxidative process that causes death is supported by the observation that zinc supplementation prevented the activation of pancreatic NFκB and the expression of iNOS (inducible nitric oxide synthase), a NFκB-dependent process. The severity of the diabetic state also was lessened in animals fed diets containing a level of zinc (500 ppm) that did not increase the pancreatic content of metallothionein, the inducible cysteine-rich zinc binding protein with antioxidant activity. This observation suggests that relatively small changes in cell zinc may protect cells against oxidative insults.

Further investigations are needed to define direct and indirect mechanisms by which zinc protects pancreatic β-cells in rodents against diabetogenic agents. Likewise, the possibility that zinc alone or in combination with other antioxidants is capable of preventing, delaying or attenuating the destruction of human β-cells merits consideration. The low toxicity of oral zinc represents a favorable feature for its use in intervention trials. Indeed, an increasing number of intervention trials have shown that zinc supplementation decreases the duration and severity of diarrhea and respiratory infections in children in developing countries where suboptimal zinc status appears to be common (3,4). The possibility that moderate zinc supplementation also may promote human pancreatic health is quite intriguing.

1. Tobia MH, Zadowicz MM, Wingertzahn MA, McHeffey-Atkinson B, Slonim AE, Wapnir RA. The role of dietary zinc in modifying the onset and severity of spontaneous diabetes in the BB Wistar rat. Mol Genet Metab 63:205-213, 1998.
2. Ho E, Quan N, Tsai YH, Lai W, Bray TM. Dietary zinc supplementation inhibits NFκB activation and protects against chemically induced diabetes in CD1 mice. Exp Biol Med 26:103-111, 2001.
3. Black RE. Therapeutic and preventative effects of zinc on serious childhood infectious diseases in developing countries. Am J Clin Nutr 68(suppl):476S-479S, 1998.
4. Strand TA, Chandyo RK, Bahl R, Sharma PR, Adhikari RK, Bhandari N, Ulvik RJ, Molbak K, Bhan MK, Sommerfelt H. Effectiveness and efficacy of zinc for the treatment of acute diarrhea in young children. Pediatrics 109:898-903, 2002.